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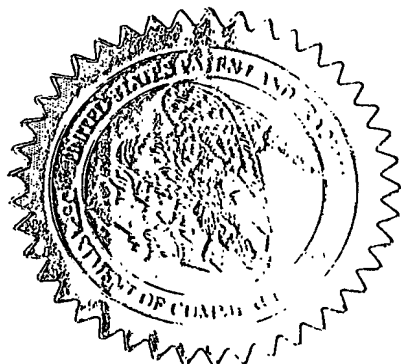
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**TITLE OF THE INVENTION**

PHARMACEUTICAL COMPOSITIONS WITH IMPROVED DISSOLUTION

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**ENCLOSED APPLICATION PARTS (check all that apply)**

- (X) Specification *Number of Pages 65*  
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( ) Additional inventors are being named on separately numbered sheets attached hereto.

**METHOD OF PAYMENT**

A check in the amount of \$ 80.00 to cover the filing fee is enclosed.

At any time during the pendency of this application, please charge any fees required or credit any overpayment to Deposit Account No. (Order No. TPIP017F+).

Respectfully submitted,

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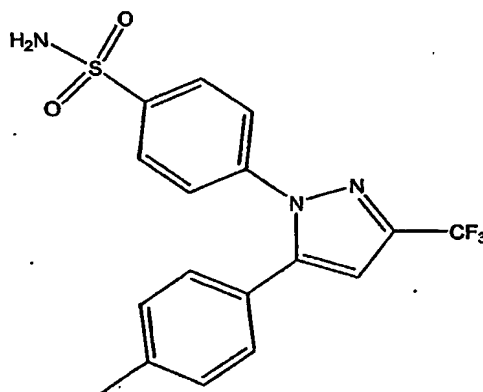
## PHARMACEUTICAL COMPOSITIONS WITH IMPROVED DISSOLUTION

### FIELD OF THE INVENTION

The present invention relates to pharmaceutical compositions and methods for preparing same.

### BACKGROUND OF THE INVENTION

Celecoxib (4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide) is a substituted pyrazolylbenzenesulfonamide represented by the structure:



Celecoxib belongs to the general class of non-steroidal anti-inflammatory drugs (NSAIDs). Unlike traditional NSAIDs, celecoxib is a selective inhibitor of cyclooxygenase II (COX-2) that causes fewer side effects when administered to a subject. The synthesis and use of celecoxib are further described in U.S. Pat. Nos. 5,466,823, 5,510,496, 5,563,165, 5,753,688, 5,760,068, 5,972,986, and 6,156,781, the contents of which are incorporated by reference in their entirety. Orally deliverable liquid formulations of celecoxib are discussed in U.S. Patent Application Publication No. 2002/0107250 in the name of Hariharan, et al., the contents of which are incorporated herein by reference in their entirety.

Other Cox-2 inhibitory drugs are related to celecoxib, which form part of a larger group of drugs, all of which are benzene sulfonamides. These include: deracoxib, which is 4-[3-fluoro-4-methoxyphenyl]-3-difluoromethyl-1H-pyrazol-1-yl]benzene sulfonamide; valdecoxib, which is 4-[5-methyl-3-phenyl isoxazol-4-yl]benzene sulfonamide; rofecoxib, which is 3-phenyl-4-[(methylsulfonyl)phenyl]-5H-furan-2-one; and etoricoxib, which is 5-chloro-3-(4-methylsulfonyl)phenyl-2-(2-methyl-5-pyridinyl)pyridine. These drugs are described in further detail in WO01/78724 and WO02/102376.

In its commercially available form as Celebrex<sup>TM</sup>, celecoxib is a neutral molecule that is essentially insoluble in water. Celecoxib typically exists as needle-like crystals, which tend to

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aggregate into a mass. Aggregation occurs even when celecoxib is mixed with other substances, such that a non-uniform mixture is obtained. These properties are shared by other pyrazolylbenzenesulfonamides and present significant problems in preparing pharmaceutical formulations of the drugs, particularly oral formulations.

It would be advantageous to provide new forms of drugs that have low aqueous dissolution which have improved properties, in particular as oral formulations. In particular, even where a drug of low aqueous solubility is provided in a form which has improved aqueous solubility, there still exists a problem when dissolution of the drug is required, for example after having been taken as an oral formulation where the drug becomes diluted in the alimentary canal. In this situation drugs having low aqueous solubility tend to come out of solution. When this happens, for example by a process of crystallization or precipitation, the bioavailability of the drug is significantly decreased. It would therefore be desirable to improve the properties of formulations containing such drugs so as to increase the bioavailability of the drug in an orally-administered form, thereby to provide a more rapid onset to therapeutic effect.

#### SUMMARY OF THE INVENTION

It has now been found that a stable, crystalline salts of celecoxib can be synthesized, e.g., a sodium salt as shown in Example 1. The celecoxib salts of the present invention have a greater solubility, dissolution, total bioavailability (area under the curve or AUC), lower  $T_{max}$ , the time to reach peak blood serum levels, and higher  $C_{max}$ , the maximum blood serum concentration, than neutral celecoxib. The celecoxib salts of the present invention when in crystalline form convert to either an amorphous free form of celecoxib upon neutralization of the salt, which subsequently converts to a neutral metastable crystalline form or directly to a neutral metastable crystalline form. These amorphous and metastable-crystalline forms of neutral celecoxib are more readily available forms of the drug than is presently-marketed neutral celecoxib. Neutral celecoxib is presently-marketed as Celebrex<sup>TM</sup>, and is designated as "neutral" to distinguish it from the ionized salt form of celecoxib. In addition, acidification or neutralization of a solution of the celecoxib salt *in situ* yields amorphous celecoxib, which subsequently converts to a metastable crystalline form or directly to a neutral metastable crystalline form of neutral celecoxib before finally converting into stable, neutral celecoxib.

An aspect of the present invention relates to methods of increasing dissolution, solubility, and or the time a pharmaceutical (the terms pharmaceutical and drug are used herein interchangeably), can be maintained, upon dissolution, as a supersaturated solution, before precipitating out of solution. The

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increase in dissolution (or concentration as a function of time) can be represented by an increase in bioavailability, AUC, reduced time to T<sub>max</sub> or increased C<sub>max</sub>. The methods comprise the steps of making a salt of a free acid pharmaceutical and combining the salt with a recrystallization retardant and optionally, a recrystallization retardant enhancer (referred to as enhancer hereafter). The salt may be amorphous or crystalline, but is preferably crystalline. Normally the salt form used is in a crystalline form which dissolves and then recrystallizes and precipitates out of solution, which is why the term "re"crystallization retardant is used. It is noted however, that one could begin with an amorphous form of the salt so the term is used when beginning with either a crystalline or amorphous form. Crystalline salts are superior to amorphous salts as the initial compound, with an amorphous salt being superior to a neutral amorphous or crystalline form. Neutral forms are not preferred initial compounds unless first solubilized in a solubilizer resulting in a liquid formulation comprising a solubilizer crystallization retardant and optional enhancer. The recrystallization retardant is often a surfactant, preferably a surfactant with an ether functional group, preferably a repeating ether group. Further preferred surfactants have an interfacial tension of less than 10 dynes per centimeter when measured at a concentration of 0.1%w/w in water as compared to mineral oil at 25°C and/or the surface tension of the recrystallization retardant (e.g., poloxamers) is less than 42 dynes/cm when measured as a concentration of 0.1%w/w in water at 25°C. The combination of salt, recrystallization retardant and an optional enhancer (or recrystallization retardant, an optional enhancer and some other form) preferably prevents or delays precipitation of a supersaturated solution by about 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, or 60 minutes or greater than 1 hour in an aqueous solution, preferably water or gastric fluid conditions such as the gastric fluids of an average human stomach fasted for 12 hours or simulated gastric fluid (SGF). Preferably, the solution remain supersaturated for more than 15, 20, or 30 minutes to allow the composition to move out of the stomach and into an environment with a higher pH. The SGF may be diluted by 2, 3, 4, 5, 6, 7, 8, 9, 10 fold to represent water intake. Normally, the SGF is diluted 5 fold to represent a patient drinking a glass of water at the time a composition of the present invention is taken orally. The degree of increase in solubility, dissolution, and/or supersaturation may be specified, such as by 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100%, or by 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350, 400, 500, 1000, 10,000, or 100,000 fold greater than neutral celecoxib in the same solution. The increase in dissolution may be further specified by the time the composition remain supersaturated.

The enhancer preferably comprises a cellulose ester such as hydroxypropylcellulose (HPC) or hydroxypropylmethylcellulose (HPMC). Thus according to the methods of the present invention,

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supersaturated concentrations upon which a drug may be maintained upon dissolution and/or the degree of dissolution of a drug in gastric fluid conditions (e.g., SGF) is enhanced. The methods of the present invention are used to make a pharmaceutical drug formulation with greater solubility, dissolution, and bioavailability, AUC, reduced time to  $T_{max}$ , the time to reach peak blood serum levels, and higher  $C_{max}$ , the maximum blood serum concentration, when compared to the neutral form or salt alone.

AUC is the area under the plot of plasma concentration of drug (not logarithm of the concentration) against time after drug administration. The area is conveniently determined by the "trapezoidal rule": the data points are connected by straight line segments, perpendiculars are erected from the abscissa to each data point, and the sum of the areas of the triangles and trapezoids so constructed is computed. When the last measured concentration ( $C_n$  at time  $t_n$ ) is not zero, the AUC from  $t_n$  to infinite time is estimated by  $C_n/k_{el}$ .

The AUC is of particular use in estimating bioavailability of drugs, and in estimating total clearance of drugs ( $Cl_T$ ). Following single intravenous doses,  $AUC = D/Cl_T$ , for single compartment systems obeying first-order elimination kinetics; alternatively,  $AUC = C_0/k_{el}$ . With routes other than the intravenous, for such systems,  $AUC = F \cdot D/Cl_T$ , where  $F$  is the availability of the drug.

The invention further relates to wherein a recrystallization retardant and an optional enhancer is combined with a pharmaceutical that is already in a salt form. The invention further relates to wherein a recrystallization retardant and an optional enhancer is combined with a pharmaceutical that is a co-crystal, solvate, desolvate, hydrate, dehydrate, or anhydrous form of a salt or neutral form.

Accordingly, in a further aspect, the present invention provides a pharmaceutical composition comprising:

- (a) a drug having low aqueous solubility or dissolution, preferably in gastric fluid conditions;
- (b) a recrystallization retardant; and
- (c) an optional enhancer.

In a further aspect, the present invention provides a pharmaceutical composition comprising:

- (a) a drug having low aqueous solubility or dissolution, preferably in gastric fluid conditions;

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- (b) a recrystallization retardant having an interfacial tension of less than 10 dyne/cm or a surface tension of less than 42 dyne/cm; and
- (c) an optional enhancer.

In a further aspect, the present invention provides a pharmaceutical composition comprising:

- (a) a drug having low aqueous solubility or dissolution, preferably in gastric fluid conditions;
- (b) a surfactant; and
- (c) an optional enhancer.

In a further aspect, the present invention provides a pharmaceutical composition comprising:

- (a) a drug having low aqueous solubility or dissolution, preferably in gastric fluid conditions;
- (b) a poloxamer having an interfacial tension of less than 10 dyne/cm or surface tension less than 42 dyne/cm; and
- (c) an optional enhancer.

In a further aspect, the present invention provides a pharmaceutical composition comprising:

- (a) a drug having low aqueous solubility or dissolution, preferably in gastric fluid conditions;
- (b) a surfactant; and
- (c) a cellulose ester.

In a further aspect, the present invention provides a pharmaceutical composition comprising:

- (a) a drug having low aqueous solubility or dissolution, preferably in gastric fluid conditions;
- (b) a surfactant having an interfacial tension of less than 10 dyne/cm or surface tension less than 42 dyne/cm; and
- (c) hydroxypropyl cellulose or hydroxypropyl methylcellulose.

In a further aspect, the present invention provides a pharmaceutical composition comprising:

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- (a) a drug having low aqueous solubility or dissolution, preferably in gastric fluid conditions;
- (b) a poloxamer; and
- (c) hydroxypropyl cellulose or hydroxypropyl methylcellulose.

In a further aspect, the present invention provides a pharmaceutical composition comprising:

- (a) a drug having low aqueous solubility or dissolution, preferably in gastric fluid conditions;
- (b) a poloxamer having an interfacial tension of less than 10 dyne/cm or surface tension less than 42 dyne/cm; and
- (c) hydroxypropyl cellulose or hydroxypropyl methylcellulose.

In a further aspect, the present invention provides a pharmaceutical composition comprising

- (a) celecoxib;
- (b) a poloxamer surfactant having an interfacial tension at a concentration of 0.1% of less than 10 dyne/cm or surface tension less than 42 dyne/cm; and
- (c) a crystallization retardant comprising a hydroxypropyl cellulose or hydroxypropyl methylcellulose.

In a further aspect, the present invention provides a process for producing a pharmaceutical composition for delivering a supersaturated concentration of a drug having low aqueous dissolution, preferably in gastric fluid conditions, which process comprises intimately mixing together the components of the above aspects or elsewhere herein.

In a further aspect, the surfactant is at a concentration of less than 5%, 4%, 3%, 2%, 1%, 0.9%, 0.8%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2%, or 0.1% or at a concentration of 0.1% (w/w).

#### **BRIEF DESCRIPTION OF THE DRAWINGS**

Fig. 1 shows a differential scanning calorimetry trace of the sodium salt of celecoxib prepared by Example 1 between 50°C and 110°C.

Fig. 2 shows a thermogravimetric analysis of the sodium salt of celecoxib prepared by Example 1, which was conducted from about 30°C to about 160°C.



Fig. 3 shows a powder x-ray diffraction plot of the sodium salt of celecoxib prepared by Example 1.

Figs. 4A and 4B show pharmacokinetics in male Sprague-Dawley rats after 5 mg/kg oral doses of the celecoxib crystal form used in the marketed formulations and the sodium salt of 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide, as obtained following the protocol described in Example 4.

Fig. 5 shows the mean pharmacokinetic parameters (and standard deviations therefor) of celecoxib in the plasma of male dogs following a single oral or single intravenous dose of celecoxib or celecoxib sodium. The maximum serum concentration and bioavailability of orally-administered celecoxib sodium was about three- and two-fold greater, respectively, than a roughly equal dose of orally-administered celecoxib, and the maximum serum concentration of celecoxib sodium was reached 40% faster than for celecoxib.

Fig. 6 shows the mean concentrations of celecoxib in plasma following the administration of a single oral dose of celecoxib or celecoxib sodium or a single intravenous dose of celecoxib in male dogs.

Fig. 7 shows the effect of varying ratios of ethylene glycol to propylene glycol subunits in poloxamers on the concentration of celecoxib sodium in solution.

Fig. 8 shows the effect of different celluloses on the dissolution of various composition comprising equal weights of cellulose (hydroxypropylcellulose (HPC, 100,000 kDa), low-viscosity hydroxypropylmethylcellulose (ld HPMC, viscosity was 80-120 cps), high-viscosity hydroxypropylmethylcellulose (hd HPMC, viscosity was 15,000 cps), microcrystalline cellulose (Avicel PH200)), d-alpha-tocopherol polyethylene glycol-1000 succinate (vitamin E TGPS), and celecoxib sodium.

Fig. 9 shows the dissolution at 37°C for compositions comprising various weight ratios of d-alpha-tocopherol polyethylene glycol-1000 succinate (vitamin E TGPS), hydroxypropylcellulose and celecoxib sodium.

Fig. 10 shows the dissolution profile of celecoxib sodium in simulated gastric fluid (SGF) from solid mixtures with excipients at room temperature. The legend indicates the excipient and the weight ratio of excipient to celecoxib sodium (if unmarked, 1:1). Excipients include polyvinylpyrrolidone (PVP), poloxamer 188 (P188), poloxamer 237 (P237), d-alpha-tocopherol polyethylene glycol-1000 succinate (vit E TGPS), and Gelucire™ 50/13.

Fig. 11 shows the effect of Avicel microcrystalline cellulose and silica gel on the dissolution of mixtures of celecoxib sodium, d-alpha-tocopherol polyethylene glycol-1000 succinate (vit E TGPS), and hydroxypropylcellulose (HPC) mixtures in simulated gastric fluid (SGF) at 37°C. The legend indicates the weight ratios of the components.

Fig. 12 shows the dissolution of celecoxib sodium (TPI336Na) in 5-times diluted simulated gastric fluid, with excipients including d-alpha-tocopherol polyethylene glycol-1000 succinate (vitamin E TGPS), hydroxypropylcellulose (HPC), and poloxamer 237. the legend indicates the weight ratios of the components.

Figs. 13A and 13B shows the particle-induced x-ray diffraction (PXRD) and raman spectra, respectively, of the sodium salt of celecoxib prepared by the method of Example 6.

Fig. 14 shows a differential scanning calorimetry analysis of celecoxib lithium salt MO-116-49B.

Fig. 15 shows a thermogravimetric analysis of celecoxib lithium salt MO-116-49B.

Fig. 16 shows the RAMAN spectrum of celecoxib lithium salt MO-116-49B.

Fig. 17 shows the PXRD spectrum of celecoxib lithium salt MO-116-49B.

Fig. 18 shows a differential scanning calorimetry analysis of celecoxib potassium salt MO-116-49A.

Fig. 19 shows a thermogravimetric analysis of celecoxib potassium salt MO-116-49A.

Fig. 20 shows the RAMAN spectrum of celecoxib potassium salt MO-116-49A.

Fig. 21 shows the PXRD spectrum of celecoxib potassium salt MO-116-49A.

Fig. 22 shows a thermogravimetric analysis of celecoxib potassium salt MO-116-55D.

Fig. 23 shows the RAMAN spectrum of celecoxib potassium salt MO-116-55D.

Fig. 24 shows the PXRD spectrum of celecoxib potassium salt MO-116-55D.

Fig. 25 shows a thermogravimetric analysis of celecoxib calcium salt MO-116-62A.

Fig. 26 shows the RAMAN spectrum of celecoxib calcium salt MO-116-62A.

Fig. 27 shows the PXRD spectrum of celecoxib calcium salt MO-116-62A.

Fig. 28 shows the PXRD spectrum of commercially-available celecoxib.

Fig. 29 shows the RAMAN spectrum of commercially-available celecoxib.

Fig. 30 shows crystal retardation time for celecoxib as a function of excipient in simulated gastric fluid (SGF).

Fig. 31 shows interfacial tension of selected Pluronic excipients in water.

Fig. 32 shows dissolution of celecoxib sodium hydrate from compositions containing Pluronic P123 and F127.

Fig. 33 shows dissolution of celecoxib sodium hydrate from Pluronic P123, F127 and F87, in the presence of HPC.

Fig. 34 shows dissolution of celecoxib sodium hydrate using Pluronic F127, HPC and a granulating fluid.

Fig. 35 shows dissolution of celecoxib sodium hydrate using Pluronic F127 and HPC in a compact formulation.

## DETAILED DESCRIPTION OF THE INVENTION

In its most general aspect, the present invention relates to a pharmaceutical composition that includes a drug having a low aqueous solubility, e.g., in gastric fluid conditions. Typically, low aqueous solubility in the present application refers to a compound having a solubility in water which is less than or equal to 10mg/ml, when measured at 37°C, and preferably less than or equal to 5mg/ml or 1mg/ml. "Low aqueous solubility" can further be defined as less than or equal to 900, 800, 700, 600, 500, 400, 300, 200 150 100, 90, 80, 70, 60, 50, 40, 30, 20 micrograms/ml, or further 10, 5 or 1 micrograms/ml, or further 900, 800, 700, 600, 500, 400, 300, 200 150, 100 90, 80, 70, 60, 50, 40, 30, 20, or 10 ng/ml, or less than 10 ng/ml when measured at 37°C. Further aqueous solubility can be measured in simulated gastric fluid (SGF) rather than water. SGF (non-diluted) of the present invention is made by combining 1 g/L Triton X-100 and 2 g/L NaCl in water and adjusting the pH with 200mM to obtain a solution with a final pH=1.7.

The pH may also be specified as 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3, 3.5, 4, 4.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 11.5, or 12. Drugs which have a solubility of not greater than 0.1mg/ml include some sulfonamide drugs, such as the benzene sulfonamides, particularly those pyrazolylbenzenesulfonamides discussed above, which are Cox-2 inhibitors and included in the present invention. Disclosed herein are stable crystalline metal salts of pyrazolylbenzenesulfonamides such as celecoxib. Such metal salts include alkali metal or alkaline earth metal salts, preferably sodium, potassium, lithium, calcium and magnesium salts.

The surfactant used in the present invention can be chosen from a wide range of surfactants (see e.g., Fig. 30). Embodiments include where the surfactant is non-ionic or wherein the surfactant is ionic. In embodiments of the present invention, the interfacial tension of the recrystallization retardant (e.g., poloxamers) is less than 10 dyne/cm when measured as a concentration of 0.1%w/w in water as

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compared to mineral oil at 25°C and/or the surface tension of the recrystallization retardant (e.g., poloxamers) is less than 42 dyne/cm when measured as a concentration of 0.1%w/w in water. In embodiments of the invention the interfacial tension above is less than 15, 14, 13, 12, 11, 9, 8, 7, or 6 dynes/cm or the surface tension is above is less than 45, 44, 43, 41, 40, 39, 38, 37, 36, or 35 dynes/cm. In other embodiments, the surfactant is a poloxamer. A poloxamer comprises an ethylene oxide-propylene oxide block copolymer, which preferably has the structure  $(\text{PEG})_x\text{-(PPG)}_y\text{-(PEG)}_z$ , where x, y and z are integers and x is usually equal to z. A preferred form of poloxamer are those obtainable from BASF designated "Pluronic"®. The invention is not, however, limited to the Pluronic series as similar poloxamers obtainable from other sources may be used. Preferred Pluronic poloxamers according to the invention include Pluronic L122, Pluronic P123, Pluronic F127 (Poloxamer 407), Pluronic L72, Pluronic P105, Pluronic LP2, Pluronic P104, Pluronic F108 (Poloxamer 338), or Pluronic P103.

The optional third component of the pharmaceutical composition according to the present invention comprises a recrystallization retardant enhancer. An enhancer is a compound capable of increasing the effectiveness of the recrystallization retardant in inhibiting, preventing or at least reducing the extent of crystallization or precipitation of the drug of low aqueous solubility, usually when diluted such as following oral administration. In one embodiment the enhancer does not act as a recrystallization retardant alone. In another embodiment the enhancer has no affect or a negative affect in an in vitro recrystallization assay, but increases the effectiveness of the recrystallization retardant in an in vitro or in situ dissolution assay. Cellulose esters, such as hydroxypropyl cellulose are particularly useful enhancer according to the present invention. Cellulose esters vary in the chain length of their cellulosic backbone and consequently, in their viscosity as measured for example at a 2% by weight concentration in water at 20 degrees C. Lower viscosities are normally preferred to higher viscosities in the present invention. In embodiments of the present invention the cellulose ester, such as HPC, has a viscosity, 2% in water, of about 100 to about 100,000 cP or about 1000 to about 15,000 cP. In other embodiments the viscosity is less than 1,500,000, 1,000,000, 500,000, 100,000, 75,000, 50,000, 35,000, 25,000, 20,000, 17,500, 15,000, 12,500, 11,000, 10,500, 9,000, 8,000, 7,000, 6,000, 5,000, 4,000, 3,000, 2,000, 1,000, 750, 500, or 250 cP, or has a viscosity in a range selected from any two preceding integers.

Enhancers are also useful in delaying the T<sub>max</sub> and/or increasing the amount of time the drug concentration is above ½ T<sub>max</sub>, thus acting to smooth out the curve. Preferred enhancers increase the

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amount of time the drug concentration is above  $\frac{1}{2}$  T<sub>max</sub> by 25%, 50%, 75%, 100%, three fold or more than three fold.

The ratio of component a:b:c (drug: recrystallization retardant;enhancer) as exemplified herein is approximately 1:1:1 (+/- 0.2 for the recrystallization retardant and enhancer). However, the ratio can be adjusted to suit the application. For example, the amount of recrystallization retardant or enhance may need to be decreased, and even decreased below the optimum concentration in order to decrease the amount of excipients in the administered form of the composition, such as a tablet or capsule.

The composition may further comprise a pharmaceutically-acceptable diluent, excipient or carrier and such additional components are discussed in further detail below. One such additional component comprises a granulating fluid-like liquid, such as poloxamer 124, PEG 200 or PEG 400, that forms an intimate contact between the drug, recrystallization retardant and optional enhancer by binding or partially dissolving them. Preferably the composition remains in a solid, semi-solid or paste, although an embodiment is drawn to wherein the composition is at least 25%, 50%, 75% or nearly or fully dissolved. Any pharmaceutically acceptable liquid may be used as long as it does not cause conversion of the salt form to the free form in the solid state. Some non-limiting examples include methanol, ethanol, isopropanol, higher alcohols, propylene glycol, ethyl caprylate, propylene glycol laurate, PEG, diethyl glycol monoethyl ether (DGME), tetraethylene glycol dimethyl ether, triethylene glycol monoethyl ether, and polysorbate 80. The presence of the granulated fluid-like liquid increases the dissolution of the drug, possibly by delaying the contact between the drug and the dissolution medium until the surfactant dissolves to a significant extent, thus delaying recrystallization. The use of a granulating fluid-like liquid is particularly useful when the drug and recrystallization retardant are solids.

As an alternative embodiment to increase supersaturation of the drug, the pharmaceutical composition is in the form of a compact whereby, during the process of producing the pharmaceutical composition, the components are compacted together. Compaction may perform a similar role to that performed by the granulating fluid. Retarded dissolution may be limited, if required, by using a disintegrant in the compact.

In a further embodiment the drug and crystallization retardant (and optional enhancer), when mixed forms a paste or non-aqueous solution. An adherent mass of components may be produced if a paste is used which is thought to delay dissolution of the drug by allowing the surfactant to dissolve first. This is thought to promote dissolution of the drug.

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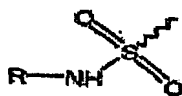
Normally the compound(s) and the drug on the present invention are intimately associated with the pharmaceutical. An "intimate association" in the present context includes, for example, the pharmaceutical admixed with the crystallization inhibitor, the pharmaceutical embedded or incorporated in the crystallization inhibitor, the compound forming a coating on particles of the pharmaceutical or vice versa, and a substantially homogeneous dispersion of the pharmaceutical throughout the compound(s).

Where the pharmaceutical composition includes a Cox-2 inhibitor, a method of treating a subject is provided in a further aspect of the invention, in which the subject may be suffering from pain, inflammation, cancer or pre-cancer such as intestinal or colonic polyps. The method comprises administering to the subject a pharmaceutical composition as described herein.

It is preferred that the pharmaceutical composition is formulated for oral administration. Drugs according to the invention may be prepared in a form having an increased time to onset of therapeutic effectiveness and likely having increased bioavailability. The pharmaceutical compositions according to the invention are therefore particularly suitable for administration to human subjects.

The methods and compositions of the present invention relate to improving solubility, dissolution and bioavailability of pharmaceuticals. The present invention further relates to improving the performance of pharmaceutical compounds that are free acids in their neutral state or that initially dissolve but then recrystallize in gastric fluid conditions. Further embodiments relate to pharmaceuticals with an aminosulfonyl functional group.

The term "aminosulfonyl functional group" herein refers to a functional group having the following structure:



wherein the wavy line represents a bond by which the functional group is attached to the rest of the drug molecule; and R is hydrogen or a substituent that preserves ability of polyethylene glycol or a polyethylene glycol degradation product to react with the

amino group adjacent to R to form an addition compound. Illustrative examples of such substituents include partially unsaturated heterocyclyl, heteroaryl, cycloalkenyl, aryl, alkylcarbonyl, formyl, halo, alkyl, haloalkyl, oxo, cyano, nitro, carboxyl, phenyl, alkoxy, aminocarbonyl, alkoxycarbonyl, carboxyalkyl, cyanoalkyl, hydroxyalkyl, hydroxyl, alkoxyalkyloxyalkyl, haloalkylsulfonyloxy, carboxyalkoxyalkyl, cycloalkylalkyl, alkynyl, heterocyclyloxy, alkylthio, cycloalkyl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, heteroarylcarbonyl, alkylthioalkyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, aralkoxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, alkylaminocarbonyl, N-arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylaminocarbonylalkyl, alkylamino, N-arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-arylaminino, aminoalkyl, alkylaminoalkyl, N-arylaminalkyl, N-aralkylaminalkyl, N-alkyl-N-aralkylaminalkyl, N-alkyl-N-arylaminalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, etc.

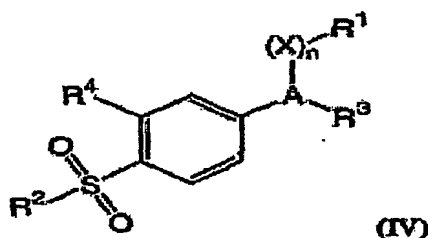
Non-limiting illustrative examples of aminosulfonyl-comprising drugs include ABT-751 of Eisai (N-(2-((4-hydroxyphenyl)amino)-3-pyridyl)-4-methoxybenzenesulfonamide); alpiropide; amosulalol; amprenavir; amsacrine; argatroban; asulacrine; azosemide; BAY-38-4766 of Bayer (N-[4-[[5-(dimethylamino)-1-naphthalenyl]sulfonyl]amino]phenyl]-3-hydroxy-2,2-dimethylpropanamide); bendroflumethiazide; BMS-193884 of Bristol Myers Squibb (N-(3,4-dimethyl-5-isoxazolyl)-4'-(2-oxazolyl)-[1,1'-biphenyl]-2-sulfonamide); bosentan; bumetanide; celecoxib; chlorthalidone; delavirdine; deracoxib; dofetilide; domitroban; dorzolamide; dronedarone; E-7070 of Eisai (N-(3-chloro-1H-indol-7-yl)-1,4-benzene-disulfonamide); EF-7412 of Schwartz Pharma (N-3-[4-[4-(tetrahydro-1,3-dioxo-1H-pyrrolo[1,2-c]imidazol-2(3H)-yl)butyl]-1-piperazinyl]phenyl]ethanesulfonamide); fenquizone; furosemide; glibenclamide; glidazide; glimepiride; glipentide; glipizide; gliquidone; glisolamide; GW-8510 of Glaxo SmithKline (4-[[6,7-dihydro-7-oxo-8H-pyrrolo[2,3-g]benzothiazol-8-ylidene)methyl]amino]-N-2-pyridinylbenzenesulfonamide); GYKI-16638 of Ivax (N-[4-[2-[[2-(2,6-dimethoxyphenoxy)-1-methylethyl]methylamino]ethyl]phenyl]methanesulfonamide); HMR-1098 of Aventis (5-chloro-2-methoxy-N-[2-[4-methoxy-3-[[[(methylamino)thioxomethyl]amino]sulfonyl]phenyl]ethyl]benzamide); hydrochlorthiazide; ibutilide; indapamide; IS-741 of Ishihara (N-[2-[(ethylsulfonyl)

amino]-5-(trifluoromethyl)-3-pyridinyl]cyclohexanecarboxamide); JTE-S22 of Japan Tobacco (4-(4-cyclohexyl-2-methyl-5-oxazolyl)-2-fluorobenzenesulfonamide); KCB-328 of Chugai (N-[3-amino-4-[2-[(2-(3,4-dimethoxyphenyl)ethyl)methylamino]ethoxy]phenyl]methanesulfonamide); KT2-962 of Kotobuki (3-[4-[(4-chlorophenyl)sulfonyl]amino]butyl]-6-(1-methylethyl)-1-azulene sulfonic acid); levosulpiride; LY-295501 (N-[(3,4-dichlorophenyl)amino]carbonyl]-2,3-dihydro-5-benzofuransulfonamide) and LY-404187 (N-2-(4-(4-cyanophenyl)phenyl)propyl-2-propanesulfonamide) of Eli Lilly; metolazone; naratriptan; nimesulide; NS-49 of Nippon ((R)-N-[3-(2-amino-1-hydroxyethyl)-4-fluorophenyl]methanesulfonamide); ONO-8711 of Ono ((5Z)-6-[(2R,3S)-3-[[[(4-chloro-2-methylphenyl)sulfonyl]amino]methyl]bicyclo[2.2.2]oct-2-yl]-5-hexenoic acid); pirtanide; PNU-103657 of Pharmacia (1-[5-methanesulfonamidoindol-2-ylcarbonyl]-4-(N-methyl-N-(3-(2-methylpropyl)-2-pyridinyl)amino)piperidine); polythiazide; ramatroban; RO-61-1790 of Hoffmann LaRoche (N-[6-(2-hydroxyethoxy)-5-(2-methoxyphenoxy)-2-[2-(1H-tetrazol-5-yl)-4-pyridinyl]-4-pyrimidinyl]-5-methyl-2-pyridinesulfonamide); RPR-130737 (4-hydroxy-3-[2-oxo-3(S)-[5-(3-pyridyl)thiophen-2-ylsulfonamido]pyrrolidin-1-ylmethyl]benzamide) and RPR-208707 of Aventis; S-18886 (3-[(6-(4-chlorophenyl)sulfonylamino)-2-methyl-5,6,7,8-tetrahydronaphth]-1-yl)propionic acid) and S-32080 (3-[6-(4-chlorophenyl)sulfonylamido)-2-propyl-3-(3-pyridyl-methyl)-5,6,7,8-tetrahydronaphthalen-1-yl]propionic acid) of Servier; S-36496 of Kaken (2-sulfonyl-[N-(4-chlorophenyl)sulfonylamino-butyl-N-[(4-cyclobutylthiazol-2-yl)ethenylphenyl-3-yl-methyl]]aminobenzoic acid); sampatrilat; SB-203208 of Glaxo SmithKline (L-phenylalanine, b-methyl-, (4aR,6S,7R,7aS)-4-(aminocarbonyl)-7-[[[(2S,3S)-2-amino-3-methyl-1-oxopentyl]amino]sulfonyl]acetyl]amino]-7-carboxy-2,4a,5,6,7,7a-hexahydro-2-methyl-1H-cyclopenta[c]pyridin-6-yl ester, (bS)-); SE-170 of DuPont (2-(5-amidino-1H-indol-3-yl)N-[2'-(aminosulfonyl)-3-bromo(1,1'-biphenyl)-4-yl]acetamide); sivelestat; SJA-6017 of Senju (N-(4-fluorophenylsulfonyl)-L-valyl-L-leucinal); SM-19712 of Sumitomo (4-chloro-N-[[4-cyano-3-methyl-1-phenyl-1H-pyrazol-5-yl]amino]carbonyl]benzenesulfonamide); sonopirazole; sotalol; sulfadiazine; sulfaguanole; sulfasalazine; sulpiride; sulprostone; sumatriptan; T-614 of Toyama (N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl]-methanesulfonamide); T-138067 (2,3,4,5,6-



perfluoro-N-(3-fluoro-4-methoxyphenyl)benzenesulfonamide) and T-900607 (2,3,4,5,6-pentafluoro-N-(3-ureido-4-methoxyphenyl)benzenesulfonamide) of Tularik; TAK-661 of Takeda (2,2-dimethyl-3-[(7-(1-methylethyl)[1,2,4]triazolo[1,5-b]pyridazin-6-yl]oxy)-1-propanesulfonamide); tamsulosin; tezoseptan; tipranavir; tirofiban; torasemide; trichloromethiazide; tripamide; valdecoxib; veralipride; xipamide; Z-335 of Zeria (2-[2-(4-chlorophenylsulfonylaminomethyl)indan-5-yl]acetic acid); zafirlukast; zonisamide; and salts thereof.

In a preferred embodiment, the aminosulfonyl-comprising drug is a selective COX-2 inhibitory drug of low water solubility. Suitable selective COX-2 inhibitory drugs are compounds having the formula (IV):



wherein:

A is a substituent selected from partially unsaturated or unsaturated heterocyclyl and partially unsaturated or unsaturated carbocyclic rings, preferably a heterocyclyl group selected from pyrazolyl, furanonyl, isoxazolyl, pyridinyl, cyclopentenonyl and pyridazinonyl groups;

X is O, S or CH<sub>2</sub>;

n is 0 or 1;

R<sup>1</sup> is at least one substituent selected from heterocyclyl, cycloalkyl, cycloalkenyl and aryl, and is optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio;

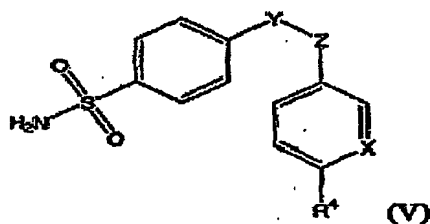
R<sup>2</sup> is an NH<sub>2</sub> group;

R<sup>3</sup> is one or more radicals selected from hydrido, halo, alkyl, alkenyl, alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocycloxy, alkyloxy, alkylthio,

alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, aralkoxyalkyl, alkoxyaralkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N-arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-arylaminalkyl, N-aralkylaminoalkyl, N-alkyl-N-aralkylaminoalkyl, N-alkyl-N-arylaminalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl and N-alkyl-N-arylaminosulfonyl,  $R^3$  being optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio; and

$R^4$  is selected from hydrido and halo.

Particularly suitable selective COX-2 inhibitory drugs are compounds having the formula (V):



where  $R^4$  is hydrogen or a  $C_{1-4}$  alkyl or alkoxy group, X is N or  $CR^5$  where  $R^5$  is hydrogen or halogen, and Y and Z are independently carbon or nitrogen atoms defining adjacent atoms of a five- to six-membered ring that is unsubstituted or substituted at one or more positions with oxo, halo, methyl or halomethyl groups. Preferred such five- to six-membered rings are cyclopentenone, furanone, methylpyrazole, isoxazole and pyridine rings substituted at no more than one position.

Illustratively, compositions of the invention are suitable for celecoxib, deracoxib, valdecoxib and JTE-522, more particularly celecoxib and valdecoxib.

In a particularly preferred embodiment, the pharmaceutical compositions of the present invention comprise a salt of celecoxib, (e.g., sodium, lithium, potassium or calcium salt). The salt may be significantly more soluble in water than presently-marketed neutral celecoxib. Due to the high  $pK_a$  of celecoxib (approximately 11), salts only form under strongly basic conditions. Typically, more than about one equivalent of a base is required to convert celecoxib to its salt form. A suitable aqueous solution for converting celecoxib to a salt has a pH of about 11.0 or greater, about 11.5 or greater, about 12 or greater, or about 13 or greater. Typically, the pH of such a solution is about 12 to about 13. Although celecoxib is a preferred embodiment, the invention includes other pharmaceutical drugs with a  $pK_a$  greater than 9, 9.5, 10, 10.5, 11, 11.5, 12, 12.5, or 13. The drug may normally be in a neutral form or a salt form may already exist.

Salts of the pharmaceutical, such as celecoxib, are formed by reaction of the pharmaceutical with an acceptable base. Acceptable bases include, but are not limited to, metal hydroxides and alkoxides. Metals include alkali metals (sodium, potassium, lithium, cesium), alkaline earth metals (magnesium, calcium), zinc, aluminum, and bismuth. Alkoxides include methoxide, ethoxide, n-propoxide, isopropoxide and t-butoxide. Additional bases include arginine, procaine, and other molecules having amino or guanidinium moieties with sufficiently high  $pK_a$ 's (e.g.,  $pK_a$ 's greater than about 11,  $pK_a$ 's greater than about 11.5, or  $pK_a$ 's greater than about 12), along with compounds having a carbon-alkali metal bond (e.g., t-butyl lithium). Sodium hydroxide and sodium ethoxide are preferred bases. The amount of base used to form a salt is typically about one or more, about two or more, about three or more, about four or more, about five or more, or about ten or more equivalents relative to the pharmaceutical. Preferably, about three to about five equivalents of one or more bases are reacted with the pharmaceutical to form a salt.

A pharmaceutical salt can be transformed into a second pharmaceutical salt by transmetallation or another process that replaces the cation of the first pharmaceutical salt. In one example, a sodium salt of pharmaceutical is prepared and is subsequently reacted with a second salt such as an alkaline earth metal halide (e.g.,  $MgBr_2$ ,  $MgCl_2$ ,  $CaCl_2$ ,  $CaBr_2$ ), an alkaline earth metal sulfate or nitrate (e.g.,  $Mg(NO_3)_2$ ,  $Mg(SO_4)_2$ ,  $Ca(NO_3)_2$ ,  $Ca(SO_4)_2$ ), or an alkaline metal salt of an organic acid (e.g. calcium formate, magnesium formate, calcium acetate, magnesium acetate, calcium propionate, magnesium propionate) to form an alkaline earth metal salt of the pharmaceutical.

In a preferred embodiment of the present invention, the pharmaceutical salts are substantially pure. A salt that is substantially pure can be greater than about 80% pure, greater than about 85% pure, greater than about 90% pure, greater than about 95% pure, greater than about 98% pure, or

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greater than about 99% pure. Purity of a salt can be measured with respect to the amount of salt (as opposed to unreacted neutral pharmaceutical or base) or can be measured with respect to a specific polymorph, co-crystal, solvate, desolvate, hydrate, dehydrate, or anhydrous form of a salt.

A pharmaceutical salt as described herein may be significantly more soluble in water than the existing neutral form, such as the presently-marketed neutral celecoxib, and is typically at least about twice, at least about three times, at least about five times, at least about ten times, at least about twenty times, at least about fifty times, or one at least about hundred times more or soluble in water or SGF than the neutral form, such as celecoxib marketed by Pfizer Inc. and G. D. Searle & Co. (Pharmacia Corporation), and described at pages 2676-2680 and 2780-2784 of the 2002 edition of the Physicians Desk Reference (also referred to herein as presently-marketed celecoxib). The solubility depends on whether the salt is tested alone, or as a formulation further comprising the recrystallization retardants and enhancers of the invention.

After dissolution, typically in an aqueous or partially-aqueous solution (e.g., where one or more polar organic solvents are a co-solvent), the salt can be neutralized by an acid or by dissolved gases such as carbon dioxide. Typically, the pH of such a solution is 11 or less, 10 or less, or 9 or less. Neutralizing the salt results in precipitation of an amorphous or metastable crystalline form of neutral celecoxib. Typically, neutralizing a pharmaceutical salt includes protonating the majority of negatively charged anions. For celecoxib, protonation results in the formation of amorphous and/or metastable crystalline celecoxib, which are "neutral" (i.e., predominantly uncharged). Preferably, the neutral pharmaceutical (including amorphous and/or metastable crystalline forms thereof, such as celecoxib) comprises 10% mol or less of charged molecules. For example, at about pH 2 (e.g., about the pH of the stomach interior), solutions of the sodium salt of celecoxib precipitate immediately as an amorphous form of neutral celecoxib. The amorphous form converts to a neutral metastable crystalline form, which subsequently becomes the stable, needle-like, insoluble form of neutral celecoxib. For example, amorphous neutral celecoxib formed from the salts of the present invention, e.g., the sodium salt of Example 1, converts to metastable crystalline neutral celecoxib over about 5 to about 10 minutes. Amorphous neutral celecoxib converts to the same more rapidly. Amorphous neutral celecoxib can be characterized by a lack of a regular crystal structure, while metastable crystalline neutral celecoxib can be distinguished from typical crystalline neutral celecoxib by the PXRD pattern of isolated material.

Amorphous and metastable crystalline forms of neutral celecoxib are more soluble and likely more readily absorbed by a subject than stable crystalline forms of neutral celecoxib, because the

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energy required for a drug molecule to escape from a stable crystal is greater than the energy required for the same drug molecule to escape from a non-crystalline, amorphous form or a metastable crystalline form. However, the instability of neutral amorphous and neutral metastable crystalline forms makes them difficult to formulate as pharmaceutical compositions. As is described in U.S. Publication No. 2002/0006951, the teachings of which are incorporated herein by reference in their entirety, without stabilization by a crystallization inhibitor, such as a polymer, amorphous and metastable crystalline neutral celecoxib convert back to a stable, insoluble crystalline form of neutral celecoxib. These teachings are incomplete and fall far short of the present invention however, as we have surprisingly found that far superior formulations can be made from the combination of a salt, recrystallization retardant, and an optional enhancer. Whereas others have focused on the initial solubilization of celecoxib, the present invention is equally concerned with dissolution and recrystallization of the drug (See e.g., WO 02/102376 and WO 01/78724). Moreover, until now, no one has disclosed a salt of celecoxib and the vital role it plays in dissolution and recrystallization. No one has further taught the addition of an enhancer to a recrystallization retardant.

Further aspects of the invention relate to liquid formulations of compounds of the present invention (e.g. celecoxib). In these aspects, the drug is solubilized either directly with the crystallization retardant or with a solubilizer or solvent. Preferred solubilizers are glycol ethers.

Glycol ethers useful as solubilizers of neutral or other forms of celecoxib include those that conform with the formula:



wherein  $R^1$  and  $R^2$  are independently hydrogen or  $C_{1-6}$  alkyl,  $C_{1-6}$  alkenyl, phenyl or benzyl groups, but no more than one of  $R^1$  and  $R^2$  is hydrogen;  $m$  is an integer of 2 to about 5; and  $n$  is an integer of 1 to about 20. It is preferred that one of  $R^1$  and  $R^2$  is a  $C_{1-4}$  alkyl group and the other is hydrogen or a  $C_{1-4}$  alkyl group; more preferably at least one of  $R^1$  and  $R^2$  is a methyl or ethyl group. It is preferred that  $m$  is 2. It is preferred that  $n$  is an integer of 1 to about 4, more preferably 2.

Glycol ethers used in compositions of the present invention typically have a molecular weight of about 75 to about 1000, preferably about 75 to about 500, and more preferably about 100 to about 300. Importantly, the glycol ethers used in compositions of the present invention must be pharmaceutically acceptable and must meet all other conditions prescribed herein.

Non-limiting examples of glycol ethers that may be used in compositions of the present invention include ethylene glycol monomethyl ether, ethylene glycol dimethyl ether, ethylene glycol monoethyl ether, ethylene glycol diethyl ether, ethylene glycol monobutyl ether, ethylene glycol dibutyl ether, ethylene glycol monophenyl ether, ethylene glycol monobenzyl ether, ethylene glycol butylphenyl ether, ethylene glycol terpinyl ether, diethylene glycol monomethyl ether, diethylene glycol dimethyl ether, diethylene glycol monoethyl ether, diethylene glycol diethyl ether, diethylene glycol divinyl ether, ethylene glycol monobutyl ether, diethylene glycol dibutyl ether, diethylene glycol monoisobutyl ether, triethylene glycol dimethyl ether, triethylene glycol monoethyl ether, triethylene glycol monobutyl ether, tetraethylene glycol dimethyl ether, and mixtures thereof. See for example Flick (1998); Industrial Solvents Handbook, 5th ed., Noyes Data Corporation, Westwood, NJ. A presently preferred glycol ether solvent is diethylene glycol monoethyl ether, sometimes referred to in the art as DGM or ethoxydiglycol. It is available for example under the trademark Transcutol™ of Galtefossé Corporation.

Compositions of the present invention optionally comprise one or more pharmaceutically acceptable co-solvents. Non-limiting examples of co-solvents suitable for use in compositions of the present invention include any glycol ether listed above; alcohols, for example ethanol and n-butanol; glycols not listed above, for

Celecoxib salts are preferred because they are stable, such that they can be formulated as pharmaceutical compositions and stored before administration to a subject. Only after dissolution and subsequent neutralization do the celecoxib salts precipitate as or transform into substantially amorphous neutral and then substantially metastable crystalline neutral forms. Preferably, dissolution and neutralization of celecoxib salts occur *in situ* in the gastrointestinal tract of a subject (e.g., stomach, duodenum, ileum), such that a maximal amount of amorphous and/or metastable crystalline neutral celecoxib is present after administration (e.g., *in vivo*), rather than before administration.

The present invention demonstrates that the length of time in which celecoxib or other drug remains in solution can be increased to a surprising high degree by using a salt form with the presence of a recrystallization retardant, normally a surfactant (e.g., poloxamer, TPGS, SDS, etc.) and an optional enhancer (e.g., hydroxypropyl cellulose) as discussed herein. The presence of these agents allows the formation of a supersaturated solution of the celecoxib salt and a high concentration of celecoxib will remain in solution for an extended period of time. The presence of these components does not preclude the presence of other further agents, including further surfactants such as, polyethyl glycol and polyoxyethylene sorbitan esters. The additional presence of other suitable surfactants is also not precluded and these are listed herein. Further additional agents which might slow the rate of precipitation such as polyvinylpyrrolidone are also not precluded. Neutral celecoxib has a solubility in water of less than 1 microgram/ml and cannot be maintained as a supersaturated solution for any appreciable time. The present invention is drawn compositions that can be maintained for a period of time (e.g., 15, 30, 45, 60, mins and longer) as supersaturated solutions at concentrations 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100%, or by 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350, 400, 500, 1000, 10,000, or 100,000 fold greater than the solubility of neutral celecoxib in the same solution (e.g., water or SGF).

The amount of recrystallization inhibitor or enhancer may each or together be less than 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 70, 80, or 90%w/w (recrystallization inhibitor or enhancer/pharmaceutical). The %w/w for either or both recrystallization inhibitor or enhancer may also be in a range represented by any two integers of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 70, 80, or 90.

Celecoxib salts of the present invention are typically stable (i.e., more than 90% of the celecoxib salt does not change in composition or crystalline structure) for at least about one week, at least about one month, at least about two months, at least about three months, at least about six months, at least about nine months, at least about one year, or at least about two years at room

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temperature in the absence of moisture. Room temperature typically ranges from about 15°C to about 30°C. The absence of moisture, as defined herein, refers to celecoxib salts not contacting quantities of liquid, particularly water or alcohols. For purposes of the present invention, gases such as water vapor are not considered to be moisture.

The uptake of a drug by a subject can also be assessed in terms of maximum blood serum concentration and time to reach maximum blood serum concentration. Pharmaceutical compositions with a more rapid onset to therapeutic effect typically reach a higher maximum blood serum concentration ( $C_{max}$ ) a shorter time after oral administration ( $T_{max}$ ). Preferably, compositions, preferably including salts, of the present invention have a higher  $C_{max}$  and/or a shorter  $T_{max}$  than presently-marketed celecoxib. The  $T_{max}$  for the compositions of the present invention may occur within about 60 minutes, 55 minutes, 50 minutes, 45 minutes, 40 minutes, 35 minutes, 30 minutes, 25 minutes, 20 minutes, 15 minutes, 10 minutes, or within about 5 minutes of administration (e.g., oral administration). Even more preferably, the therapeutic effects of compositions of the present invention begin to occur within about 60 minutes, 55 minutes, 50 minutes, 45 minutes, 40 minutes, 35 minutes, 30 minutes, within about 25 minutes, within about 20 minutes, within about 15 minutes, within about 10 minutes, or within about 5 minutes of administration (e.g., oral administration).

Compositions of the present invention have a bioavailability greater than the neutral celecoxib and currently marketed Celebrex TM. In other embodiments, the compositions of the present invention have a bioavailability of at least 50%, 60%, 65%, 70%, 75%, 80%, 85%, 87%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%.

Ailments treatable with celecoxib and salts thereof of the present invention are discussed below. Treatment of both acute and chronic pain is a preferred embodiment of the present invention.

While not being bound by theory, Applicants believe that the low solubility of presently-marketed celecoxib has an impact on other pharmaceutical properties. For example, the dose-response curve for presently-marketed celecoxib is nonlinear. Preferably, the dose-response curve for celecoxib salts is linear or contains a larger linear region than presently-marketed celecoxib. Also, the absorption or uptake of presently-marketed celecoxib depends in part on food effects, such that uptake of celecoxib increases when taken with food, especially fatty food. Preferably, uptake of celecoxib salts of the present invention exhibits a decreased dependence on food, such that the difference in uptake of celecoxib salts when taken with food and when not taken with food is less than the difference in uptake of presently-marketed celecoxib.



A celecoxib salt can be characterized by differential scanning calorimetry (DSC). The sodium salt of celecoxib prepared in Example 1 is characterized by at least 3 overlapping endothermic transitions between 50°C and 110°C (Fig. 1). Conditions for DSC can be found in Example 1.

Celecoxib salts can be characterized by thermogravimetric analysis (TGA). The sodium salt product prepared by Example 1 was characterized by TGA, and had about 3 loosely bound equivalents of water that evaporated between about 30°C and about 40°C, one more tightly bound equivalent of water that evaporated between about 40°C and about 100°C, and one very tightly bound equivalent of water that evaporated between about 140°C and about 160°C (Fig. 2). Conditions for TGA can be found in Example 1.

Celecoxib salts of the present invention can also be characterized by powder x-ray diffraction (PXRD). The sodium salt of celecoxib prepared by Example 1 had an intense reflection or peak at a 2-theta angle of 6.40°, and other reflections or peaks at 7.01°, 16.73°, and 20.93° (Fig. 3). Conditions for PXRD can be found in Example 1.

Celecoxib salts may comprise solvate molecules and can occur in a variety of solvation states, also known as solvates. Thus, celecoxib salts can exist as crystalline polymorphs. Polymorphs are different crystalline forms of the same drug substance, and in the present use of the term include solvates and hydrates. For example, different polymorphs of a celecoxib salt can be obtained by varying the method of preparation (compare Examples). Crystalline polymorphs typically have different solubilities, such that a more thermodynamically stable polymorph is less soluble than a less thermodynamically stable polymorph. Pharmaceutical polymorphs can also differ in properties such as shelf-life, bioavailability, morphology, vapor pressure, density, color, and compressibility.

Suitable solvate molecules include water, alcohols, other polar organic solvents, and combinations thereof. Alcohols include methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol, propylene glycol and t-butanol. Propylene glycol solvates are particularly preferred because they are more stable and less hygroscopic than other forms. Alcohols also include polymerized alcohols such as polyalkylene glycols (e.g., polyethylene glycol, polypropylene glycol). In an embodiment, water is the solvent. In embodiments of the invention, a celecoxib salt contains about 0.0%, less than 0.5%, 0.5, 1, less than 1%, 1.5, less than 1.5%, 2, less than 2%, 2.5, 3, 3.5, 4, 4.5, 5, 5.5 or about 6 equivalents, or about 1 to about 6, 2 to about 5, 3 to about 6, 3 to about 5, 1 to about 4, 2 to about 4, 1 to about 3, 2 to about 3, 0 to about 3, 0.5 to about 3, 0 to about 2, 0.5 to about 2, 0 to about 1.5, 0.5 to about 1.5, 1 to about 1.5, or 0.5 to about 1 equivalents of water per equivalent of salt. Solvate molecules can be removed from a crystalline salt, such that the salt is either a partial or

complete desolvate. If the solvate molecule is water (forming a hydrate), then a desolvated salt is said to be a dehydrate. A salt with all water removed is anhydrous. Solvate molecules can be removed from a salt by methods such as heating, treating under vacuum or reduced pressure, blowing dry air over a salt, or a combination thereof. Following desolvation, there are typically about one to about five equivalents, about one to about four equivalents, about one to about three equivalents, or about one to about two equivalents of solvent per equivalent of salt in a crystal.

Pharmaceuticals including celecoxib, can co-crystallize with one or more other substances. The other substance, the cocrystal former, can interact with a celecoxib salt through hydrogen bonds, pi stacking, or van der Waals interactions, a combination thereof, or other energetically-favorable manners. In embodiments of the present invention, the pharmaceutical is a co-crystal. In other embodiments the co-crystal formers are selected from one or two (for ternary co-crystals) of the following: saccharin, nicotinamide, pyridoxine (4-pyridoxic acid), acesulfame, glycine, arginine, asparagine, cysteine, glutamine, histidine, isoleucine, lysine, methionine, phenylalanine, proline, threonine, tyrosine, valine, aspartic acid, glutamic acid, tryptophan, adenine, acetohydroxamic acid, alanine, allopurinaol, 4-aminobenzoic acid, cyclamic acid, 4-ethoxyphenyl urea, 4-aminopyridine, leucine, nicotinic acid, serine, tris, vitamin k5, xylito, succinic acid, tartaric acid, pyridoxamine, ascorbic acid, hydroquinone, salicylic acid, benzoic acid, caffeine, benzenesulfonic acid, 4-chlorobenzene-sulfonic acid, citric acid, fumaric acid, gluconic acid, glutaric acid, glycolic acid, hippuric acid, maleic, malic acid, mandelic acid, malonic, 1,5-naphthalene-disulfonic acid (armstrong's acid), clemizole, imidazole, glucosamine, piperazine, procaine, or urea.

Celecoxib salts may be prepared by contacting celecoxib with a solvent. Suitable solvents include water, alcohols, other polar organic solvents, and combinations thereof. Water and isopropanol are preferred solvents. Celecoxib is reacted with a base, where suitable bases are listed above, such that celecoxib forms a salt and preferably dissolves. Bases can be added to celecoxib with the solvent (i.e., dissolved in the solvent), such that celecoxib is solvated and deprotonated essentially simultaneously (e.g., see Example 3), or bases can be added after the celecoxib has been contacted with solvent (e.g., see Example 1). In the latter scenario, bases can either be dissolved in a solvent, which can be either the solvent already contacting celecoxib or a different solvent, can be added as a neat solid or liquid, or a combination thereof. Sodium hydroxide and sodium ethoxide are preferred bases. The amount of base required is discussed above. The solvent can be evaporated to obtain crystals of the celecoxib salt, or the celecoxib salt may precipitate and/or crystallize independent of

evaporation. Crystals of a celecoxib salt can be filtered to remove bulk solvent. Methods of removing solvated solvent molecules are discussed above.

Excipients employed in pharmaceutical compositions of the present invention can be solids, semi-solids, liquids or combinations thereof. Preferably, excipients are solids. Compositions of the invention containing excipients can be prepared by any known technique of pharmacy that comprises admixing an excipient with a drug or therapeutic agent. A pharmaceutical composition of the invention contains a desired amount of celecoxib per dose unit and, if intended for oral administration, can be in the form, for example, of a tablet, a caplet, a pill, a hard or soft capsule, a lozenge, a cachet, a dispensable powder, granules, a suspension, an elixir, a dispersion, a liquid, or any other form reasonably adapted for such administration. If intended for parenteral administration, it can be in the form, for example, of a suspension or transdermal patch. If intended for rectal administration, it can be in the form, for example, of a suppository. Presently preferred are oral dosage forms that are discrete dose units each containing a predetermined amount of the drug, such as tablets or capsules.

Non-limiting examples follow of excipients that can be used to prepare pharmaceutical compositions of the invention.

Pharmaceutical compositions of the invention optionally comprise one or more further pharmaceutically acceptable carriers or diluents as excipients. Suitable carriers or diluents illustratively include, but are not limited to, either individually or in combination, lactose, including anhydrous lactose and lactose monohydrate; starches, including directly compressible starch and hydrolyzed starches (e.g., Celutab<sup>TM</sup> and Emdex<sup>TM</sup>); mannitol; sorbitol; xylitol; dextrose (e.g., Cerelease<sup>TM</sup> 2000) and dextrose monohydrate; dibasic calcium phosphate dihydrate; sucrose-based diluents; confectioner's sugar; monobasic calcium sulfate monohydrate; calcium sulfate dihydrate; granular calcium lactate trihydrate; dextrates; inositol; hydrolyzed cereal solids; amylose; celluloses including microcrystalline cellulose, food grade sources of alpha- and amorphous cellulose (e.g., RexcelJ), powdered cellulose, and hydroxypropylmethylcellulose (HPMC); calcium carbonate; glycine; bentonite; block co-polymers; polyvinylpyrrolidone; and the like. Such carriers or diluents, if present, constitute in total about 5% to about 99%, preferably about 10% to about 85%, and more preferably about 20% to about 80%, of the total weight of the composition. The carrier, carriers, diluent, or diluents selected preferably exhibit suitable flow properties and, where tablets are desired, compressibility.

Lactose, mannitol, dibasic sodium phosphate, and microcrystalline cellulose (particularly Avicel PH microcrystalline cellulose such as Avicel PH 101), either individually or in combination,

are preferred diluents. These diluents are chemically compatible with celecoxib. The use of extragranular microcrystalline cellulose (that is, microcrystalline cellulose added to a granulated composition) can be used to improve hardness (for tablets) and/or disintegration time. Lactose, especially lactose monohydrate, is particularly preferred. Lactose typically provides compositions having suitable release rates of celecoxib, stability, pre-compression flowability, and/or drying properties at a relatively low diluent cost. It provides a high density substrate that aids densification during granulation (where wet granulation is employed) and therefore improves blend flow properties and tablet properties.

Pharmaceutical compositions of the invention optionally comprise one or more pharmaceutically acceptable disintegrants as excipients, particularly for tablet formulations. Suitable disintegrants include, but are not limited to, either individually or in combination, starches, including sodium starch glycolate (e.g., Explotab<sup>TM</sup> of PenWest) and pregelatinized corn starches (e.g., National<sup>TM</sup> 1551 of National Starch and Chemical Company, National<sup>TM</sup> 1550, and Colocorn<sup>TM</sup> 1500), clays (e.g., Veegum<sup>TM</sup> HV of R.T. Vanderbilt), celluloses such as purified cellulose, microcrystalline cellulose, methylcellulose, carboxymethylcellulose and sodium carboxymethylcellulose, croscarmellose sodium (e.g., Ac-Di-Sol<sup>TM</sup> of FMC), alginates, crospovidone, and gums such as agar, guar, locust bean, karaya, pectin and tragacanth gums.

Disintegrants may be added at any suitable step during the preparation of the composition, particularly prior to granulation or during a lubrication step prior to compression. Such disintegrants, if present, constitute in total about 0.2% to about 30%, preferably about 0.2% to about 10%, and more preferably about 0.2% to about 5%, of the total weight of the composition.

Croscarmellose sodium is a preferred disintegrant for tablet or capsule disintegration, and, if present, preferably constitutes about 0.2% to about 10%, more preferably about 0.2% to about 7%, and still more preferably about 0.2% to about 5%, of the total weight of the composition. Croscarmellose sodium confers superior intragranular disintegration capabilities to granulated pharmaceutical compositions of the present invention.

Pharmaceutical compositions of the invention optionally comprise one or more pharmaceutically acceptable binding agents or adhesives as excipients, particularly for tablet formulations. Such binding agents and adhesives preferably impart sufficient cohesion to the powder being tableted to allow for normal processing operations such as sizing, lubrication, compression and packaging, but still allow the tablet to disintegrate and the composition to be absorbed upon ingestion. Such binding agents may also further prevent or inhibit crystallization or recrystallization of a

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celecoxib salt of the present invention once the salt has been dissolved in a solution. Suitable binding agents and adhesives include, but are not limited to, either individually or in combination, acacia; tragacanth; sucrose; gelatin; glucose; starches such as, but not limited to, pregelatinized starches (e.g., National<sup>TM</sup> 1511 and National<sup>TM</sup> 1500); celluloses such as, but not limited to, methylcellulose and carmellose sodium (e.g., Tylose<sup>TM</sup>); alginic acid and salts of alginic acid; magnesium aluminum silicate; PEG; guar gum; polysaccharide acids; bentonites; povidone, for example povidone K-15, K-30 and K-29/32; polymethacrylates; HPMC; hydroxypropylcellulose (e.g., Klucel<sup>TM</sup> of Aqualon); and ethylcellulose (e.g., Ethocel<sup>TM</sup> of the Dow Chemical Company). Such binding agents and/or adhesives, if present, constitute in total about 0.5% to about 25%, preferably about 0.75% to about 15%, and more preferably about 1% to about 10%, of the total weight of the pharmaceutical composition.

Many of the binding agents are polymers comprising amide, ester, ether, alcohol or ketone groups and, as such, are preferably included in pharmaceutical compositions of the present invention. Polyvinylpyrrolidones such as povidone K-30 are especially preferred. Polymeric binding agents can have varying molecular weight, degrees of crosslinking, and grades of polymer. Polymeric binding agents can also be copolymers, such as block co-polymers that contain mixtures of ethylene oxide and propylene oxide units. Variation in these units' ratios in a given polymer affects properties and performance. Examples of block co-polymers with varying compositions of block units are Poloxamer 188 and Poloxamer 237 (BASF Corporation).

Pharmaceutical compositions of the invention optionally comprise one or more pharmaceutically acceptable wetting agents as excipients. Such wetting agents are preferably selected to maintain the celecoxib in close association with water, a condition that is believed to improve bioavailability of the composition. Such wetting agents can also be useful in solubilizing or increasing the solubility of metal salts of celecoxib.

Non-limiting examples of surfactants that can be used as wetting agents (not necessarily as the recrystallization retardant) in pharmaceutical compositions of the invention include quaternary ammonium compounds, for example benzalkonium chloride, benzethonium chloride and cetylpyridinium chloride, dioctyl sodium sulfosuccinate, polyoxyethylene alkylphenyl ethers, for example nonoxynol 9, nonoxynol 10, and octoxynol 9, poloxamers (polyoxyethylene and polyoxypropylene block copolymers), polyoxyethylene fatty acid glycerides and oils, for example polyoxyethylene (8) caprylic/capric mono- and diglycerides (e.g., Labrasol<sup>TM</sup> of Gattefosse), polyoxyethylene (35) castor oil and polyoxyethylene (40) hydrogenated castor oil; polyoxyethylene

alkyl ethers, for example polyoxyethylene (20) cetostearyl ether, polyoxyethylene fatty acid esters, for example polyoxyethylene (40) stearate, polyoxyethylene sorbitan esters, for example polysorbate 20 and polysorbate 80 (e.g., Tween<sup>TM</sup> 80 of ICI), propylene glycol fatty acid esters, for example propylene glycol laurate (e.g., Lauroglycol<sup>TM</sup> of Gattefosse), sodium lauryl sulfate, fatty acids and salts thereof, for example oleic acid, sodium oleate and triethanolamine oleate, glyceryl fatty acid esters, for example glyceryl monostearate, sorbitan esters, for example sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate and sorbitan monostearate, tyloxapol, and mixtures thereof. Such wetting agents, if present, constitute in total about 0.25% to about 15%, preferably about 0.4% to about 10%, and more preferably about 0.5% to about 5%, of the total weight of the pharmaceutical composition.

Wetting agents that are anionic surfactants are preferred. Sodium lauryl sulfate is a particularly preferred wetting agent. Sodium lauryl sulfate, if present, constitutes about 0.25% to about 7%, more preferably about 0.4% to about 4%, and still more preferably about 0.5% to about 2%, of the total weight of the pharmaceutical composition.

Pharmaceutical compositions of the invention optionally comprise one or more pharmaceutically acceptable lubricants (including anti-adherents and/or glidants) as excipients. Suitable lubricants include, but are not limited to, either individually or in combination, glyceryl behapate (e.g., Compritol<sup>TM</sup> 888 of Gattefosse); stearic acid and salts thereof, including magnesium, calcium and sodium stearates; hydrogenated vegetable oils (e.g., Sterotex<sup>TM</sup> of Abitec); colloidal silica; talc; waxes; boric acid; sodium benzoate; sodium acetate; sodium fumarate; sodium chloride; DL-leucine; PEG (e.g., Carbowax<sup>TM</sup> 4000 and Carbowax<sup>TM</sup> 6000 of the Dow Chemical Company); sodium oleate; sodium lauryl sulfate; and magnesium lauryl sulfate. Such lubricants, if present, constitute in total about 0.1% to about 10%, preferably about 0.2% to about 8%, and more preferably about 0.25% to about 5%, of the total weight of the pharmaceutical composition.

Magnesium stearate is a preferred lubricant used, for example, to reduce friction between the equipment and granulated mixture during compression of tablet formulations.

Suitable anti-adherents include, but are not limited to, talc, cornstarch, DL-leucine, sodium lauryl sulfate and metallic stearates. Talc is a preferred anti-adherent or glidant used, for example, to reduce formulation sticking to equipment surfaces and also to reduce static in the blend. Talc, if present, constitutes about 0.1% to about 10%, more preferably about 0.25% to about 5%, and still more preferably about 0.5% to about 2%, of the total weight of the pharmaceutical composition.

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Glidants can be used to promote powder flow of a solid formulation. Suitable glidants include, but are not limited to, colloidal silicon dioxide, starch, talc, tribasic calcium phosphate, powdered cellulose and magnesium trisilicate. Colloidal silicon dioxide is particularly preferred. Other excipients such as colorants, flavors and sweeteners are known in the pharmaceutical art and can be used in pharmaceutical compositions of the present invention. Tablets can be coated, for example with an enteric coating, or uncoated. Compositions of the invention can further comprise, for example, buffering agents.

Optionally, one or more effervescent agents can be used as disintegrants and/or to enhance organoleptic properties of pharmaceutical compositions of the invention. When present in pharmaceutical compositions of the invention to promote dosage form disintegration, one or more effervescent agents are preferably present in a total amount of about 30% to about 75%, and preferably about 45% to about 70%, for example about 60%, by weight of the pharmaceutical composition.

According to a particularly preferred embodiment of the invention, an effervescent agent, present in a solid dosage form in an amount less than that effective to promote disintegration of the dosage form, provides improved dispersion of the celecoxib in an aqueous medium. Without being bound by theory, it is believed that the effervescent agent is effective to accelerate dispersion of celecoxib from the dosage form in the gastrointestinal tract, thereby further enhancing absorption and rapid onset of therapeutic effect. When present in a pharmaceutical composition of the invention to promote intragastric dispersion but not to enhance disintegration, an effervescent agent is preferably present in an amount of about 1% to about 20%, more preferably about 2.5% to about 15%, and still more preferably about 5% to about 10%, by weight of the pharmaceutical composition.

An "effervescent agent" herein is an agent comprising one or more compounds which, acting together or individually, evolve a gas on contact with water. The gas evolved is generally oxygen or, most commonly, carbon dioxide. Preferred effervescent agents comprise an acid and a base that react in the presence of water to generate carbon dioxide gas. Preferably, the base comprises an alkali metal or alkaline earth metal carbonate or bicarbonate and the acid comprises an aliphatic carboxylic acid.

Non-limiting examples of suitable bases as components of effervescent agents useful in the invention include carbonate salts (e.g., calcium carbonate), bicarbonate salts (e.g., sodium bicarbonate), sesquicarbonate salts, and mixtures thereof. Calcium carbonate is a preferred base.

Non-limiting examples of suitable acids as components of effervescent agents and/or solid organic acids useful in the invention include citric acid, tartaric acid (as D-, L-, or D/L-tartaric acid),

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malic acid, maleic acid, fumaric acid, adipic acid, succinic acid, acid anhydrides of such acids, acid salts of such acids, and mixtures thereof. Citric acid is a preferred acid.

In a preferred embodiment of the invention, where the effervescent agent comprises an acid and a base, the weight ratio of the acid to the base is about 1:100 to about 100:1, more preferably about 1:50 to about 50:1, and still more preferably about 1:10 to about 10:1. In a further preferred embodiment of the invention, where the effervescent agent comprises an acid and a base, the ratio of the acid to the base is approximately stoichiometric.

Excipients which solubilize metal salts of celecoxib typically have both hydrophilic and hydrophobic regions, or are preferably amphiphilic or have amphiphilic regions. One type of amphiphilic or partially-amphiphilic excipient comprises an amphiphilic polymer or is an amphiphilic polymer. A specific amphiphilic polymer is a polyalkylene glycol, which is commonly comprised of ethylene glycol and/or propylene glycol subunits. Such polyalkylene glycols can be esterified at their termini by a carboxylic acid, ester, acid anhydride or other suitable moiety. Examples of such excipients include poloxamers (symmetric block copolymers of ethylene glycol and propylene glycol; e.g., poloxamer 237), polyalkylene glycolated esters of tocopherol (including esters formed from a di- or multi-functional carboxylic acid; e.g., d-alpha-tocopherol polyethylene glycol-1000 succinate), and macrogolglycerides (formed by alcoholysis of an oil and esterification of a polyalkylene glycol to produce a mixture of mono-, di- and tri-glycerides and mono- and di-esters; e.g., stearyl macrogol-32 glycerides). Such pharmaceutical compositions are advantageously administered orally.

Pharmaceutical compositions of the present invention can comprise about 10% to about 50%, about 25% to about 50%, about 30% to about 45%, or about 30% to about 35% by weight of a metal salt of celecoxib; about 10% to about 50%, about 25% to about 50%, about 30% to about 45%, or about 30% to about 35% by weight of an excipient which inhibits crystallization; and about 5% to about 50%, about 10% to about 40%, about 15% to about 35%, or about 30% to about 35% by weight of a binding agent. In one example, the weight ratio of the metal salt of celecoxib to the excipient which inhibits crystallization to binding agent is about 1 to 1 to 1.

Solid dosage forms of the invention can be prepared by any suitable process, not limited to processes described herein.

An illustrative process comprises (i) a step of blending a celecoxib salt of the invention with one or more excipients to form a blend, and (ii) a step of tableting or encapsulating the blend to form tablets or capsules, respectively.



In a preferred process, solid dosage forms are prepared by a process comprising (a) a step of blending the celecoxib salt to form a blend, (b) a step of granulating the blend to form a granulate, and (c) a step of tableting or encapsulating the blend to form tablets or capsules respectively. Step (b) can be accomplished by any dry or wet granulation technique known in the art. A celecoxib salt is advantageously granulated to form particles of about 1 micrometer to about 100 micrometer, about 5 micrometer to about 50 micrometer, or about 10 micrometer to about 25 micrometer. One or more diluents, one or more disintegrants and one or more binding agents may be added, for example in the blending step, a wetting agent can optionally be added, for example in the granulating step, and one or more disintegrants may be added after granulating but before tableting or encapsulating. A lubricant may be added before tableting. Blending and granulating can be performed independently under low or high shear. A process is preferably selected that forms a granulate that is uniform in drug content, that readily disintegrates, that flows with sufficient ease so that weight variation can be reliably controlled during capsule filling or tableting, and that is dense enough in bulk so that a batch can be processed in the selected equipment and individual doses fit into the specified capsules or tablet dies.

In an alternative embodiment, solid dosage forms are prepared by a process that includes a spray drying step, wherein a celecoxib salt is suspended with one or more excipients in one or more sprayable liquids, preferably a non-protic (e.g., non-aqueous or non-alcoholic) sprayable liquid, and then is rapidly spray dried over a current of warm air.

A granulate or spray dried powder resulting from any of the above illustrative processes can be compressed or molded to prepare tablets or encapsulated to prepare capsules. Conventional tableting and encapsulation techniques known in the art can be employed. Where coated tablets are desired, conventional coating techniques are suitable.

Excipients for tablet compositions of the invention are preferably selected to provide a disintegration time of less than about 30 minutes, preferably about 25 minutes or less, more preferably about 20 minutes or less, and still more preferably about 15 minutes or less, in a standard disintegration assay.

Celecoxib dosage forms of the invention preferably comprise celecoxib in a daily dosage amount of about 10 mg to about 1000 mg, more preferably about 50 mg to about 100 mg, about 100mg to about 150 mg, 150 mg to about 200 mg, 200mg to about 250 mg, 250 mg to about 300 mg, 300 mg to about 350 mg, 350 mg to about 400 mg, 400mg to about 450 mg 450mg to about 500 mg, 500mg to about 550 mg, 550 mg to about 600 mg, 600 to about 700, and 700 to about 800 mg.

Pharmaceutical compositions of the invention comprise one or more orally deliverable dose units. Each dose unit comprises celecoxib in a therapeutically effective amount that is preferably those listed. The term "dose unit" herein means a portion of a pharmaceutical composition that contains an amount of a therapeutic or prophylactic agent, in the present case celecoxib, suitable for a single oral administration to provide a therapeutic effect. Typically one dose unit, or a small plurality (up to about 4) of dose units, in a single administration provides a dose comprising a sufficient amount of the agent to result in the desired effect. Administration of such doses can be repeated as required, typically at a dosage frequency of 1, 2, 3 or 4 times per day.

It will be understood that a therapeutically effective amount of celecoxib for a subject is dependent *inter alia* on the body weight of the subject. A "subject" to which a celecoxib salt or a pharmaceutical composition thereof can be administered includes a human subject of either sex and of any age, and also includes any nonhuman animal, particularly a warm-blooded animal, more particularly a domestic or companion animal, illustratively a cat, dog or horse. When the subject is a child or a small animal (e.g., a dog), for example, an amount of celecoxib (measured as the neutral form of celecoxib, that is, not including counterions in a salt or water in a hydrate) relatively low in the preferred range of about 10 mg to about 1000 mg is likely to provide blood serum concentrations consistent with therapeutic effectiveness. Where the subject is an adult human or a large animal (e.g., a horse), achievement of such blood serum concentrations of celecoxib is likely to require dose units containing a relatively greater amount of celecoxib.

Typical dose units in a pharmaceutical composition of the invention contain about 10, 20, 25, 37.5, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350 or 400 mg of celecoxib. For an adult human, a therapeutically effective amount of celecoxib per dose unit in a composition of the present invention is typically about 50 mg to about 400 mg. Especially preferred amounts of celecoxib per dose unit are about 100 mg to about 200 mg, for example about 100 mg or about 200 mg. Other doses that are not in current use for Celebrex<sup>TM</sup> may become preferred, if the bioavailability is changed with a novel formulation. For instance, 300 mg may become a preferred dose for certain indications.

A dose unit containing a particular amount of celecoxib can be selected to accommodate any desired frequency of administration used to achieve a desired daily dosage. The daily dosage and frequency of administration, and therefore the selection of appropriate dose unit, depends on a variety of factors, including the age, weight, sex and medical condition of the subject, and the nature and severity of the condition or disorder, and thus may vary widely.

For pain management, pharmaceutical compositions of the present invention can be used to provide a daily dosage of celecoxib of about 50 mg to about 1000 mg, preferably about 100 mg to about 600 mg, more preferably about 150 mg to about 500 mg, and still more preferably about 175 mg to about 400 mg, for example about 200 mg. A daily dose of celecoxib of about 0.7 to about 13 mg/kg body weight, preferably about 1.3 to about 8 mg/kg body weight, more preferably about 2 to about 6.7 mg/kg body weight, and still more preferably about 2.3 to about 5.3 mg/kg body weight, for example about 2.7 mg/kg body weight, is generally appropriate when administered in a pharmaceutical composition of the invention. The daily dose can be administered in one to about four doses per day. Administration at a rate of one 50 mg dose unit four times a day, one 100 mg dose unit or two 50 mg dose units twice a day or one 200 mg dose unit, two 100 mg dose units or four 50 mg dose units once a day is preferred.

The term "oral administration" herein includes any form of delivery of a therapeutic agent or a composition thereof to a subject wherein the agent or composition is placed in the mouth of the subject, whether or not the agent or composition is immediately swallowed, although each are embodiments of the invention. Thus, "oral administration" includes buccal and sublingual as well as esophageal administration. Absorption of the agent can occur in any part or parts of the gastrointestinal tract including the mouth, esophagus, stomach, duodenum, ileum and colon. The term "orally deliverable" herein means suitable for oral administration.

Pharmaceutical compositions of the invention are useful in treatment and prevention of a very wide range of disorders mediated by COX-2, including but not restricted to disorders characterized by inflammation, pain and/or fever. Such pharmaceutical compositions are especially useful as anti-inflammatory agents, such as in treatment of arthritis, with the additional benefit of having significantly less harmful side effects than compositions of conventional non-steroidal anti-inflammatory drugs (NSAIDs) that lack selectivity for COX-2 over COX-1. In particular, pharmaceutical compositions of the invention have reduced potential for gastrointestinal toxicity and gastrointestinal irritation including upper gastrointestinal ulceration and bleeding, reduced potential for renal side effects such as reduction in renal function leading to fluid retention and exacerbation of hypertension, reduced effect on bleeding times including inhibition of platelet function, and possibly a lessened ability to induce asthma attacks in aspirin-sensitive asthmatic subjects, by comparison with compositions of conventional NSAIDs. Thus compositions of the invention are particularly useful as an alternative to conventional NSAIDs where such NSAIDs are contraindicated, for example in subjects with peptic ulcers, gastritis, regional enteritis, ulcerative colitis, diverticulitis or with a

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recurrent history of gastrointestinal lesions; gastrointestinal bleeding, coagulation disorders including anemia such as hypoprothrombinemia, hemophilia or other bleeding problems; kidney disease; or in subjects prior to surgery or subjects taking anticoagulants.

Contemplated pharmaceutical compositions are useful to treat a variety of arthritic disorders, including but not limited to rheumatoid arthritis, spondyloarthropathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus and juvenile arthritis.

Such pharmaceutical compositions are useful in treatment of asthma, bronchitis, menstrual cramps, preterm labor, tendonitis, bursitis, allergic neuritis, cytomegalovirus infectivity, apoptosis including HIV-induced apoptosis, lumbago, liver disease including hepatitis, skin-related conditions such as psoriasis, eczema, acne, burns, dermatitis and ultraviolet radiation damage including sunburn, and post-operative inflammation including that following ophthalmic surgery such as cataract surgery or refractive surgery.

Pharmaceutical compositions of the present invention are useful to treat gastrointestinal conditions such as, but not limited to, inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome and ulcerative colitis.

Such pharmaceutical compositions are useful in treating inflammation in such diseases as migraine headaches, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, sclerodoma, rheumatic fever, type I diabetes, neuromuscular junction disease including myasthenia gravis, white matter disease including multiple sclerosis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis, nephritis, hypersensitivity, swelling occurring after injury including brain edema, myocardial ischemia, and the like.

In addition, these pharmaceutical compositions are useful in treatment of ophthalmic diseases, such as retinitis, conjunctivitis, retinopathies, uveitis, ocular photophobia, and of acute injury to the eye tissue.

Also, such pharmaceutical compositions are useful in treatment of pulmonary inflammation, such as that associated with viral infections and cystic fibrosis, and in bone resorption such as that associated with osteoporosis.

The pharmaceutical compositions are useful for treatment of certain central nervous system disorders, such as cortical dementias including Alzheimer's disease, neurodegeneration, and central nervous system damage resulting from stroke, ischemia and trauma. The term "treatment" in the present context includes partial or total inhibition of dementias, including Alzheimer's disease,

vascular dementia, multi-infarct dementia, pre-senile dementia, alcoholic dementia and senile dementia.

Such pharmaceutical compositions are useful in treatment of allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome and liver disease.

Further, pharmaceutical compositions of the present invention are useful in treatment of pain, including but not limited to postoperative pain, dental pain, muscular pain, and pain resulting from cancer. For example, such compositions are useful for relief of pain, fever and inflammation in a variety of conditions including rheumatic fever, influenza and other viral infections including common cold, low back and neck pain, dysmenorrhea, headache, toothache, sprains and strains, myositis, neuralgia, synovitis, arthritis, including rheumatoid arthritis, degenerative joint diseases (osteoarthritis), gout and ankylosing spondylitis, bursitis, burns, and trauma following surgical and dental procedures.

The present invention is further directed to a therapeutic method of treating a condition or disorder where treatment with a COX-2 inhibitory drug is indicated, the method comprising oral administration of a pharmaceutical composition of the invention to a subject in need thereof. The dosage regimen to prevent, give relief from, or ameliorate the condition or disorder preferably corresponds to once-a-day or twice-a-day treatment, but can be modified in accordance with a variety of factors. These include the type, age, weight, sex, diet and medical condition of the subject and the nature and severity of the disorder. Thus, the dosage regimen actually employed can vary widely and can therefore deviate from the preferred dosage regimens set forth above. The present pharmaceutical compositions can be used in combination with other therapies or therapeutic agents, including but not limited to, therapies with opioids and other analgesics, including narcotic analgesics, Mu receptor antagonists, Kappa receptor antagonists, non-narcotic (i.e. non-addictive) analgesics, monoamine uptake inhibitors, adenosine regulating agents, cannabinoid derivatives, GABA active agents, norexin neuropeptide modulators, Substance P antagonists, neurokinin-1 receptor antagonists and sodium channel blockers, among others. Preferred combination therapies comprise use of a composition of the invention with one or more compounds selected from aceclofenac, acemetacin, e-acetamidocaproic acid, acetaminophen, acetaminosalol, acetanilide, acetylsalicylic acid (aspirin), S-adenosylmethionine, alclofenac, alfentanil, allylprodine, alminoprofen, aloxiprin, alphaprodine, aluminum bis(acetylsalicylate), amfenac, aminochlorthenoxazin, 3-amino-4-hydroxybutyric acid, 2-amino-4-picoline, aminopropylon, aminopyrine, amixetrine, ammonium salicylate, ampiroxicam, amtolmetin guacil, anileridine, antipyrine, antipyrine salicylate, antrafenine, apazone, bendazac, benorylate,

benoxaprofen, benzpiperylon, benzydamine, benzylmorphine, bermoprofen, bezitramide, alpha-bisabolol, bromfenac, p-bromoacetanilide, 5-bromosalicylic acid acetate, bromosaligenin, buccetin, bucloxic acid, buclome, bufexamac, bumadizon, buprenorphine, butacetin, butibufen, butophanol, calcium acetylsalicylate, carbamazepine, carbiphen, carprofen, carsalam, chlorobutanol, chlorthenoxazin, choline salicylate, cinchophen, cinmetacin, ciramadol, clidanac, clometacin, clonitazene, clonixin, clopirac, clove, codeine, codeine methyl bromide, codeine phosphate, codeine sulfate, cropropamide, crotethamide, desomorphine, dexoxadrol, dextromoramide, dezocine, diampromide, diclofenac sodium, difenamizole, difenpiramide, diflunisal, dihydrocodeine, dihydrocodeinone enol acetate, dihydromorphine, dihydroxyaluminum acetylsalicylate, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, diprocetyl, dipyrone, ditazol, droxicam, emorfazone, enfenamic acid, epirizole, eptazocine, etersalate, ethenzamide, ethoheptazine, ethoxazene, ethylmethylthiambutene, ethylmorphine, etodolac, etofenamate, etonitazene, eugenol, felbinac, fenbufen, fenclozic acid, fendosal, fenoprofen, fentanyl, fentiazac, fepradinol, feprazone, floctafenine, flufenamic acid, flunoxaprofen, fluoresone, flupirtine, fluproquazone, flurbiprofen, fosfosal, gentisic acid, glafenine, glucametacin, glycol salicylate, guaiazulene, hydrocodone, hydromorphone, hydroxypethidine, ibufenac, ibuprofen, ibuproxam, imidazole salicylate, indomethacin, indoprofen, isofezolac, isoladol, isomethadone, isonixin, isoxepac, isoxicam, ketobemidone, ketoprofen, ketorolac, p-lactophenetide, lefetamine, levorphanol, lofentanil, lonazolac, lomoxicam, loxoprofen, lysine acetylsalicylate, magnesium acetylsalicylate, meclofenamic acid, mefenamic acid, meperidine, meptazinol, mesalamine, metazocine, methadone hydrochloride, methotrimoprazine, metiazinic acid, metofoline, metopon, modafinil, mofebutazone, mofezolac, morazone, morphine, morphine hydrochloride, morphine sulfate, morpholine salicylate, myrophine, nabumetone, nalbuphine, 1-naphthyl salicylate, naproxen, narceine, nefopam, nicomorphine, nifenazone, niflumic acid, nimesulide, 5'-nitro-2'-propoxyacetanilide, norlevorphanol, normethadone, normorphine, norpipanone, olsalazine, opium, oxaceprol, oxametacine, oxaprozin, oxycodone, oxymorphone, oxyphenbutazone, papaveretum, paranyline, parsahnide, pentazocine, perisoxal, phenacetin, phenadoxone, phenazocine, phenazopyridine hydrochloride, phenocoll, phenoperidine, phenopyrazone, phenyl acetylsalicylate, phenylbutazone, phenyl salicylate, phenyramidol, piketoprofen, piminodine, pipebuzone, piperylone, pirofen, pirazolac, piritramide, piroxicam, pranoprofen, proglumetacin, proheptazine, promedol, propacetamol, propiram, propoxyphene, propyphenazone, proquazone, protizinic acid, ramifenazone, remifentanil, rimazolium metilsulfate, salacetamide, salicin, salicylamide, salicylamide o-acetic acid, salicylsulfuric acid, salsalte, salverine,

simetride, sodium salicylate, sufentanil, sulfasalazine, sulindac, superoxide dismutase, suprofen, suxibuzone, talniflumate, tenidap, tenoxicam, terofenamate, tetrandrine, thiazolinobutazone, tiaprofenic acid, tiaramide, tilidine, tinoridine, tolfenamic acid, tolmetin, topiramate, tramadol, tropesin, viminol, xenbucin, ximoprofen, zaltoprofen and zomepirac (see The Merck Index, 12th Edition, Therapeutic Category and Biological Activity Index, ed. S. Budavari (1996), pp. Ther-2 to Ther-3 and Ther-12 (Analgesic (D)ental), Analgesic (Narcotic), Analgesic (Non-narcotic), Anti-inflammatory (Non-steroidal)).

Pharmaceutical compositions of the present invention are useful for treating and preventing inflammation-related cardiovascular disorders, including vascular diseases, coronary artery disease, aneurysm, vascular rejection, arteriosclerosis, atherosclerosis including cardiac transplant atherosclerosis, myocardial infarction, embolism, stroke, thrombosis including venous thrombosis, angina including unstable angina, coronary plaque inflammation, bacterial-induced inflammation including Chlamydia-induced inflammation, viral induced inflammation, and inflammation associated with surgical procedures such as vascular grafting including coronary artery bypass surgery, revascularization procedures including angioplasty, stent placement, endarterectomy, or other invasive procedures involving arteries, veins and capillaries.

These pharmaceutical compositions are also useful in treatment of angiogenesis-related disorders in a subject, for example to inhibit tumor angiogenesis. Such pharmaceutical compositions are useful in treatment of neoplasia, including metastasis; ophthalmological conditions such as corneal graft rejection, ocular neovascularization, retinal neovascularization including neovascularization following injury or infection, diabetic retinopathy, macular degeneration, retrolental fibroplasia and neovascular glaucoma; ulcerative diseases such as gastric ulcer; pathological, but non-malignant, conditions such as hemangiomas, including infantile hemangiomas, angiofibroma of the nasopharynx and avascular necrosis of bone; and disorders of the female reproductive system such as endometriosis.

Moreover, pharmaceutical compositions of the present invention are useful in prevention and treatment of benign and malignant tumors and neoplasia including cancer, such as colorectal cancer, brain cancer, bone cancer, epithelial cell-derived neoplasia (epithelial carcinoma) such as basal cell carcinoma, adenocarcinoma, gastrointestinal cancer such as lip cancer, mouth cancer, esophageal cancer, small bowel cancer, stomach cancer, colon cancer, liver cancer, bladder cancer, pancreatic cancer, ovarian cancer, cervical cancer, lung cancer, breast cancer, skin cancer such as squamous cell and basal cell cancers, prostate cancer, renal cell carcinoma, and other known cancers that effect epithelial cells throughout the body. Neoplasias for which compositions of the invention are

contemplated to be particularly useful are gastrointestinal cancer, Barrett's esophagus, liver cancer, bladder cancer, pancreatic cancer, ovarian cancer, prostate cancer, cervical cancer, lung cancer, breast cancer and skin cancer. Such pharmaceutical compositions can also be used to treat fibrosis that occurs with radiation therapy. These pharmaceutical compositions can be used to treat subjects having adenomatous polyps, including those with familial adenomatous polyposis (FAP). Additionally, pharmaceutical compositions of the present invention can be used to prevent polyps from forming in subjects at risk of FAP.

Also, the pharmaceutical compositions inhibit prostanoid-induced smooth muscle contraction by inhibiting synthesis of contractile prostanoids and hence can be of use in treatment of dysmenorrhea, premature labor, asthma and eosinophil-related disorders. They also can be of use for decreasing bone loss particularly in postmenopausal women (i.e., treatment of osteoporosis), and for treatment of glaucoma.

Preferred uses for pharmaceutical compositions of the invention are for treatment of rheumatoid arthritis and osteoarthritis, for pain management generally (particularly post-oral surgery pain, post-general surgery pain, post-orthopedic surgery pain, and acute flares of osteoarthritis), for treatment of Alzheimer's disease, and for colon cancer chemoprevention. A particular preferred use is for rapid pain management, such as when a celecoxib salt or a pharmaceutical composition thereof is effective in treating pain within about 30 minutes or less.

Besides being useful for human treatment, pharmaceutical compositions of the invention are useful for veterinary treatment of companion animals, exotic animals, farm animals, and the like, particularly mammals. More particularly, pharmaceutical compositions of the invention are useful for treatment of COX-2 mediated disorders in horses, dogs and cats.

#### **EXEMPLIFICATION**

Below are standard procedures for acquiring Raman, XRD, DSC and TGA data herein. These procedures will be followed for each respective method of analysis herein unless otherwise indicated.

##### **Procedure for Raman Acquisition, Filtering and Binning**

###### *Acquisition*

The sample was either left in the glass vial in which it was processed or an aliquot of the sample was transferred to a glass slide. The glass vial or slide was positioned in the sample chamber. The measurement was made using an Almega™ Dispersive Raman (Almega™ Dispersive Raman,



Thermo-Nicolet, 5225 Verona Road, Madison, WI 53711-4495) system fitted with a 785nm laser source. The sample was manually brought into focus using the microscope portion of the apparatus with a 10x power objective (unless otherwise noted), thus directing the laser onto the surface of the sample. The spectrum was acquired using the parameters outlined in Table 1. (Exposure times and number of exposures may vary; changes to parameters will be indicated for each acquisition.)

### *Filtering and Binning*

Each spectrum in a set was filtered using a matched filter of feature size 25 to remove background signals, including glass contributions and sample fluorescence. This is particularly important as large background signal or fluorescence limit the ability to accurately pick and assign peak positions in the subsequent steps of the binning process. Filtered spectra were binned using the peak pick and bin algorithm with the parameters given in Table 2. The sorted cluster diagrams for each sample set and the corresponding cluster assignments for each spectral file were used to identify groups of samples with similar spectra, which was used to identify samples for secondary analyses.

Table 1. Raman Spectral acquisition parameters

Parameter	Setting Used
Exposure time (s)	2.0
Number of exposures	10
Laser source wavelength (nm)	785
Laser power (%)	100
Aperture shape	pin hole
Aperture size (um)	100
Spectral range	104-3428
Grating position	Single
Temperature at acquisition (°C)	24.0

Table 2. Raman Filtering and Binning Parameters

Parameter	Setting Used
<i>Filtering Parameters</i>	
Filter type	Matched
Filter size	25
<i>QC Parameters</i>	
Peak Height Threshold	1000
Region for noise test (cm <sup>-1</sup> )	0-10000

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1)	
RMS noise threshold	10000
Automatically eliminate failed spectra	Yes
<i>Region of Interest</i>	
Include (cm <sup>-1</sup> )	104-3428
Exclude region I (cm <sup>-1</sup> )	
Exclude region II (cm <sup>-1</sup> )	
Exclude region III (cm <sup>-1</sup> )	
Exclude region IV (cm <sup>-1</sup> )	
<i>Peak Pick Parameters</i>	
Peak Pick Sensitivity	Variable
Peak Pick Threshold	100
<i>Peak Comparison Parameters</i>	
Peak Window (cm <sup>-1</sup> )	2
<i>Analysis Parameters</i>	
Number of clusters	Variable

#### Procedure for X-Ray Powder Diffraction

All x-ray powder diffraction patterns were obtained using the D/Max Rapid X-ray Diffractometer (D/Max Rapid, Contact Rigaku/MS, 9009 New Trails Drive, The Woodlands, Texas, USA 77381-5209) equipped with a copper source (Cu/K<sub>α</sub> 1.5406Å), manual x-y stage, and 0.3mm collimator. The sample was loaded into a 0.3mm boron rich glass capillary tube (e.g., Charles Supper Company, 15 Tech Circle, Natick Massachusetts 01760-1024) by sectioning off one end of the tube and tapping the open, sectioned end into a bed of the powdered sample or into the sediment of a slurried precipitate. Note, precipitate can be amorphous or crystalline. The loaded capillary was mounted in a holder that was secured into the x-y stage. A diffractogram was acquired (e.g., Control software: RINT Rapid Control Software, Rigaku Rapid/XRD, version 1.0.0, © 1999 Rigaku Co.) under ambient conditions at a power setting of 46kV at 40mA in reflection mode, while oscillating about the omega-axis from 0 - 5 degrees at 1 degree/s and spinning about the phi-axis at 2 degrees/s. The exposure time was 15 minutes unless otherwise specified. The diffractogram obtained was integrated over 2-theta from 2-60 degrees and chi (1 segment) from 0-360 degrees at a step size of 0.02 degrees using the *cyllnt* utility in the RINT Rapid display software (Analysis software: RINT Rapid display software, version 1.18, Rigaku/MS.) provided by Rigaku with the instrument. The dark counts value was set to 8 as per the system calibration (System set-up and calibration by Rigaku); normalization was set to average; the omega offset was set to 180°; and no chi or phi offsets were used.

for the integration. The analysis software JADE XRD Pattern Processing, versions 5.0 and 6.0 (©1995-2002, Materials Data, Inc. was also used.

#### Procedure for Differential Thermal Analysis (DSC)

An aliquot of the sample was weighed into an aluminum sample pan. (e.g., Pan part # 900786.091; lid part # 900779.901; TA Instruments, 109 Lukens Drive, New Castle, DE 19720) The sample pan was sealed either by crimping for dry samples or press fitting for wet samples (e.g., hydrated or solvated samples). The sample pan was loaded in to the apparatus (DSC: Q1000 Differential Scanning Calorimeter, TA Instruments, 109 Lukens Drive, New Castle, DE 19720), which is equipped with an autosampler, and a thermogram was obtained by individually heating the sample (e.g., Control software: Advantage for QW- Series, version 1.0.0.78, Thermal Advantage Release 2.0, © 2001 TA instruments – Water LLC) at a rate of 10°C /min from  $T_{\min}$  (typically 20°C) to  $T_{\max}$  (typically 300°C) (Heating rate and temperature range may vary, changes to these parameters will be indicated for each sample) using an empty aluminum pan as a reference. Dry nitrogen (e.g., Compressed nitrogen, grade 4.8, BOC Gases, 575 Mountain Avenue, Murray Hill, NJ 07974-2082) was used as a sample purge gas and was set at a flow rate of 50 ml/min. Thermal transitions were viewed and analyzed using the analysis software (Analysis Software: Universal Analysis 2000 for Windows 95/95/2000/NT, version 3.1E; Build 3.1.0.40, © 1991 - 2001TA instruments – Water LLC) provided with the instrument.

#### Procedure for Thermogravimetric Analysis (TGA)

An aliquot of the sample was transferred into a platinum sample pan. (Pan part # 952019.906; TA Instruments, 109 Lukens Drive, New Castle, DE 19720) The pan. was placed on the loading platform and was then automatically loaded in to the apparatus (TGA: Q500 Thermogravimetric Analyzer, TA Instruments, 109 Lukens Drive, New Castle, DE 19720) using the control software (Control software: Advantage for QW- Series, version 1.0.0.78, Thermal Advantage Release 2.0, © 2001 TA instruments – Water LLC). Thermograms were obtained by individually heating the sample at 10°C /min from 25°C to 300°C (Heating rate and temperature range may vary, changes in parameters will be indicated for each sample) under flowing dry nitrogen (e.g., Compressed nitrogen, grade 4.8, BOC Gases, 575 Mountain Avenue, Murray Hill, NJ 07974-2082), with a sample purge flow rate of 60ml/min and a balance purge flow rate of 40ml/min. Thermal transitions (e.g. weight changes) were

viewed and analyzed using the analysis software (Analysis Software: Universal Analysis 2000 for Windows 95/95/2000/NT, version 3.1E; Build 3.1.0.40, © 1991 - 2001TA instruments – Water LLC) provided with the instrument.

#### Example 1

##### Celecoxib sodium salt from aqueous solution

To 77.3 mg of commercially-available celecoxib was added 1.0 mL distilled water, followed by 0.220 mL of 1 M NaOH (VWR). The mixture was heated with stirring to 60°C, whereupon an additional 1.0 mL distilled water was added. Solid NaOH (22 mg) was added, and the solid NaOH and celecoxib dissolved. The mixture was heated again at 60°C to evaporate water. About 15 mL reagent-grade ethanol was added, while the mixture was stirred and heated at 60°C with air blowing over the solution. Heating continued until the solution was dry. The resulting material was analyzed by powder x-ray diffraction (PXRD), differential scanning calorimetry (DSC), and thermogravimetric analysis (TGA), the results of which are seen in Figs. 1-3. The product was found to contain about 4.1 equivalents of water per equivalent of salt, although most of all of the water could be contained in the NaOH that co-precipitated with the salt.

For the DSC analysis, the purge gas used was dry nitrogen, the reference material was an empty aluminum pan that was crimped, and the sample purge was 50 mL/minute. DSC analysis of the sample was performed by placing 2.594 mg of sample in an aluminum pan with a crimped pan closure. The starting temperature was 20°C with a heating rate of 10°C/minute, and the ending temperature was 200°C. The resulting DSC analysis is shown in Fig. 1. The transitions observed include a melt/dehydration process between about 40 and about 70 C, another transition between about 70 and about 100 C possibly resulting from a recrystallization event and a second melt/dehydration transition between about 100 and about 110 C.

For all of the TGA experiments, the purge gas used was dry nitrogen, the balance purge was 40 mL/minute N<sub>2</sub>, and the sample purge was 60 mL/minute N<sub>2</sub>. TGA of the sample was performed by placing 2.460 mg of sample in a platinum pan. The starting temperature was 20°C with a heating rate of 10°C/minute, and the ending temperature was 300°C. The resulting TGA analysis is shown in Fig. 2. The TGA shows a mass loss of about 12.5% between about 30 and about 50 C, attributed to the loss of about 2.8 water molecules. A second mass loss of about 2.0% between about 71 and 85 C, attributed to the loss of about 0.5 water molecules. Finally, a mass loss of about 4.0% between about

148 and 170 C attributed to either the loss of about 1 water molecule or some decomposition of the drug compound.

The PXRD pattern for the compound prepared above is shown in Fig. 3. In the diffractogram of Fig. 3, the background has been removed. The PXRD pattern has characteristic peaks comprising any one, any two, any three or all four peaks at a 2-theta angle of 6.40°, 7.01°, 16.73°, and 20.93° or of Fig. 3.

#### Example 2

##### Celecoxib sodium salt from 2-propanol solution

To 126.3 mg of celecoxib (Fako Hazlari) was added a 1.0 mL aliquot of isopropanol, and the mixture was heated to dissolve the celecoxib. Sodium ethoxide was added as a solution 21% in ethanol (0.124 mL solution,  $3.31 \times 10^{-4}$  mol sodium ethoxide). An additional 1.0 mL of isopropanol was added. The mixture was stirred to obtain a slurry of white crystalline solids that appeared as fine birefringent needles by polarized light microscopy.

The slurry was filtered by suction filtration and rinsed with 2 mL of isopropanol. The solid was allowed to air dry before being gently ground to a powder. The product was analyzed by PXRD, DSC, and TGA as in Example 1, but a 0.5 mm capillary was used to hold the sample in the PXRD experiment. The compound lost 17.35% weight between room temperature and 120°C. The DSC trace shows a broad endothermic region, which is consistent with a loss of volatile components with increasing temperature. The endotherm peaks at 66°C. The PXRD pattern has characteristic peaks comprising any two, any three, any four, or all five 2-theta angles of 4.09°, 4.99°, 6.51°, 9.99°, and 11.59°.

#### Example 3

##### Celecoxib sodium salt from aqueous solution

*Synthesis 1:* To a vial was added 29.64 mg celecoxib and 3.00 mL of 1 N sodium hydroxide. The celecoxib dissolved immediately. After a time, the celecoxib precipitated from solution.

*Synthesis 2:* To a vial was added 7.10 mg celecoxib and 3.00 mL of 1 N sodium hydroxide. The celecoxib dissolved. Overnight, the celecoxib precipitated and formed white, needle-like crystals.

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**Synthesis 3:** To a vial was added 17.6 mg celecoxib and 10 mL of 1 N sodium hydroxide. The celecoxib dissolved. The vial was placed in a beaker wrapped in aluminum foil and filled with a large tissue for insulation. The beaker was left and crystals formed within about 12-36 hours.

**Analysis:** The product solids from syntheses 1 and 2 were combined and analyzed by PXRD, DSC, and TGA as in example 1, but a 0.5 mm capillary was used to hold the sample in the PXRD experiment. The product salt was found to contain about 4 equivalents of water per equivalent of salt. TGA showed a weight loss of 14.9% as the temperature was increased from room temperature to 100°C at 10°C/min. DSC analysis showed a large endothermic transition at 74+/-1.0°C and a second broad and noisy endothermic transition at about 130+/- 5.0°C. The PXRD pattern has characteristic peaks comprising any two, any three, any four, any five, or all six 2-theta angles of 3.6°, 8.9°, 9.6°, 10.8°, 11.4°, and 20.0°.

#### Example 4

##### Pharmacokinetic Studies in Rats

The sodium salt form (from Example 6) was compared with Celebrex powder in terms of absorption in rats (Figs. 4A and 4B).

Pharmacokinetics in male Sprague-Dawley rats after 5 mg/kg oral doses of the celecoxib crystal form used in the marketed formulations and the sodium salt form are shown in Fig. 4A and 4B. Solids were placed in size 9 gelatin capsules (Torpac) and dosed via gavage needle, followed by oral gavage of 1 mL water. Celebrex® granulation was transferred from commercial 200 mg capsules. The sodium salt was blended with Povidone K30 (4:1 weight ratio to the sodium salt of celecoxib). The plots are averages of plasma levels at each of the time points from plasma of 5 rats.

The pharmacokinetics at 5 mg/kg doses of celecoxib or the celecoxib sodium salt demonstrate a faster peak level of the drug in plasma. Early timepoints show higher levels of celecoxib in plasma from the sodium salt relative to Celebrex® (in particular, see Fig. 4A).

#### Example 5

##### Solubility of Celecoxib Sodium in the Presence of Polyvinylpyrrolidone

Water was added to a 1:4 mixture of celecoxib sodium and polyvinylpyrrolidone (PVP) to obtain a clear solution. The solution was stable for at least 15 minutes, after which time crystals of neutral celecoxib began to form.

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Crystalline neutral celecoxib did not dissolve when added to aqueous polyvinylpyrrolidone or when water was added to a dry blend of neutral crystalline celecoxib and polyvinylpyrrolidone.

#### Example 6

##### Preparation of Celecoxib Sodium

The free acid of Celecoxib (5.027 g) was suspended in an aqueous solution of NaOH (13.181 mL, 1 M). The suspension was gently heated at 60°C for 1 minute to dissolve the remaining solid. The mixture was allowed to cool to room temperature, which yielded no precipitation. Further cooling in an ice bath for 1 hour gives precipitation of the product. The resulting solution was filtered and allowed to air dry.

Characterization of the product has been achieved via TGA, DSC, PXRD, Raman spectroscopy, microscopy, and <sup>1</sup>H NMR spectroscopy. NMR acquisitions were performed on a Varian 300 MHz Spectrometer in (methyl sulfoxide)-d<sup>6</sup>.

The PXRD pattern has characteristic peaks as shown in Fig. 13A. An intense peak can be seen at 19.85 with other peaks at 2-theta angles including but not limited to, 3.57, 10.69, 13.69, 20.43, and 21.53. The crystal can be characterized by any one, any two, any three, any four, or all five of the peaks above, or any one or combination of 2-theta angles of Fig. 13A.

Results of Raman spectroscopy can be seen in Fig. 13B. Raman shift (cm<sup>-1</sup>) peaks occur at positions including, but not limited to, any two, any three, any four, all five of 1617.11, 1446.20, 1373.73, 975.02 and 800.15, or any combinations 2, 3, 4, 5 or more peaks of Fig. 13B.

#### Example 7

##### Administration of celecoxib compositions to dogs

The celecoxib salt of Example 6 was administered to dogs and compared to administration of commercially available celecoxib. Six male beagle dogs aged 2-4 years old and weighing 8-12 kg were food-deprived but were given water. Each of the dogs was administered 3 test doses as described below and allowed a one week washout period between doses. The test doses were: (1) commercially available celecoxib in the form of Celebrex ® at 1 milligrams per kilograms (mpk) combined with 70/30 PEG400/water which was administered IV, (2) oral dose of commercially available celecoxib in the form of Celebrex ® at 5 mpk adjusted for each dog's weight in size 4 gelatin capsules, and (3) oral dose of the

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sodium salt of the instant invention as prepared according to Example 6 at 5 mpk adjusted for each dog's weight in size 4 gelatin capsules. Blood samples of approximately 2 ml in sodium heparin were obtained by jugular venipuncture at 0.25, 0.5, 1, 3, 4, 6, 8, 12, and 24 hours post-dose. Additional samples were obtained predose and at 0.08 hr for the IV study. Blood samples were immediately placed on ice and centrifuged within 30 min of collection at 3200 g at 4 degrees C nominal for 10 minutes. Plasma samples (~1.0 ml) were harvested and stored in 4 aliquots of 0.25 ml at -20 degrees C. Plasma samples were analyzed for celecoxib using a LC-MS/MS assay with a lower limit of quantitation of 5 ng/ml. Pharmacokinetic profiles of celecoxib in plasma were analyzed using the PhAST software Program (Version 2.3, Pheonix Life Sciences, Inc.). The absolute bioavailability (F) is reported for oral doses relative to the IV dose.

Fig. 5 shows the mean pharmacokinetic parameters (and standard deviations therefore) of celecoxib in the plasma of male dogs following a single oral or single intravenous dose of celecoxib or celecoxib sodium. The maximum serum concentration and bioavailability of orally-administered celecoxib sodium was about three- and two-fold greater, respectively, than a roughly equal dose of orally-administered celecoxib, and the maximum serum concentration of celecoxib sodium was reached 40% faster than for celecoxib.

#### Example 8

##### Celecoxib-Lithium Salt Preparation Method: MO-116-49B

To 100mg of commercially available Celecoxib was added 0.35M LiOH(aq) (Lithium Hydroxide Monohydrate – Aldrich Cat#25,427-4, Lot 00331K1) solution with a Lithium:celecoxib ratio of 1.53:1 in a vial with a Teflon coated silicon rubber septum cap. The mixture was gently heated during dissolution with occasional swirling until all solids dissolved. Flowing dry nitrogen was blown over the solution for 2 days through stainless steel needles inserted into the septum cap until the solution was dry. Characterization of the product was achieved via DSC (Fig. 14), TGA (Fig. 15), Raman spectroscopy (Fig. 16) and PXRD (Fig. 17).

##### Celecoxib-Lithium Salt Data (DSC)



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1.56mg of collected sample was placed into an aluminum DSC pan with cover. During heating, 50ml/min nitrogen purge gas was used. Results of the DSC thermogram (Fig. 14) show a melting point at 111.84 degrees C and a second endotherm, less sharp at 237.11 degrees C.

#### Celecoxib-Lithium Salt Data (TGA)

8.2290mg of collected sample was placed into a platinum TGA pan. Results of the TGA (Fig. 15) demonstrated about a 14% weight loss between about 25 degrees C and 190 degrees C.

#### Celecoxib-Lithium Salt (MO-116-49A) Data (Raman)

A small quantity of collected sample was placed on a glass slide and mounted in the Thermo Nicolet Almae Dispersive Raman. The sample capture was set to 6 background scans and 12 sample collection scans. The parameters used for this analysis were:

DATA COLLECTION INFORMATION	SPECTROMETER DESCRIPTION
Exposure time: 2.00 sec	Spectrometer: Visible Raman Microscope
Number of exposures: 12	Laser: 785 nm
Number of background exposures: 6	Laser power level: 100%
	Laser polarization: Parallel
	Grating: 360 lines/mm
	Spectrograph aperture: 100 $\mu$ m slit
	Sample position: Microscope
	Camera temperature: -50 C
	CCD rows binned: 89-150
	CCD binning: On chip
	RIM position: Mirror
	Polarization analyzer: Out
	Illuminators: Of

Results of Raman spectroscopy can be seen in Fig. 16. Raman shift ( $\text{cm}^{-1}$ ) peaks occur at positions including, but not limited to, any two, any three, any four, any five or all six of the peaks: 1617.10, 1596.95, 1449.56, 1374.03, 976.50, or 800.67, or any combinations of 2, 3, 4, 5 or more peaks of Fig. 16.

#### Celecoxib-Lithium Salt Data (PXRD)

A small amount of collected sample was placed in a 0.3mm glass PXRD tube. The tube was placed into a Rigaku D/Max Rapid PXRD and set to: Cu; 46kV/40mA; Collimeter:0.3; Omega-axis oscillation, Pos(deg) 0-5, speed 1; Phi-axis spin, Pos 360, Speed 2; Collection time was equal to 15 minutes. The PXRD pattern has characteristic peaks as shown in Fig. 17. Peaks can be seen at 2-theta

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angles including, but not limited to, 4.14, 9.04, 10.71, 12.47, 15.08, 20.52, and 21.55. The crystal can be characterized by any one, any two, any three, any four, any five, any six or all seven of the above angles or any one or combination of 2-theta angles of Fig. 17.

#### Example 9

##### Celecoxib-Potassium Salt: Preparation Method MO-116-49A

100mg of Celecoxib (Fako Ilacari A.S.) was dissolved in a 0.35M KOH(aq) solution (Potassium Hydroxide – Spectrum, Cat# P0180, Lot#PN0690) with a Potassium:Celecoxib ratio of 1.40:1 in a vial with a Teflon coated silicon rubber septum cap. The resulting solution was gently warmed during dissolution with occasional swirling until all solids dissolved. After all solids were dissolved, the solution was dried by flowing dry nitrogen over the solution for 2 days through stainless steel needles inserted into the septum cap. Analysis of the resulting product was performed. Characterization of the product was achieved via DSC (Fig. 18,) TGA (Fig. 19), Raman spectroscopy (Fig. 20) and PXRD (Fig. 21).

##### Celecoxib-Potassium Salt (MO-116-49A) Data (DSC)

1.119 mg of collected sample was placed into an aluminum DSC pan with cover. The results are depicted in the graph of Fig. 18 and show a melting point endotherm at 87.39 degrees C.

##### Celecoxib-Potassium Salt (MO-116-49A) Data (TGA)

5.9890 mg of collected sample was placed into a platinum TGA pan. The pan was placed in TA Instruments Q500 TGA and heated 10°C/min to 90°C, held for 10 minutes, ramped 10°C/min to 300°C, and held for 10 minutes with 40ml/min nitrogen purge gas. The results are depicted in Fig. 19 and show a 5.778% weight loss between 25 and 200 degrees C. A shoulder in the data is seen at 80 degrees C. Weight loss before this point is due to unbound water. The weight loss between 80 and 200 degrees C is due to more closely bound water, and represents 0.64 equivalents of water.

##### Celecoxib-Potassium Salt (MO-116-49A) Data (Raman)

A small quantity of collected sample was placed on a glass slide and mounted in the Thermo Nicolet Almega Dispersive Raman. The sample capture was set to 6 background scans and 12 sample collections. The parameters used for this analysis were:

DATA COLLECTION INFORMATION	SPECTROMETER DESCRIPTION
Exposure time: 2.00 sec	Spectrometer: Visible Raman Microscope
Number of exposures: 12	Laser: 785 nm
Number of background exposures: 6	Laser power level: 100%
	Laser polarization: Parallel
	Grating: 360 lines/mm
	Spectrograph aperture: 100 $\mu$ m slit
	Sample position: Microscope
	Camera temperature: -50 C
	CCD rows binned: 89-150
	CCD binning: On chip
	RIM position: Mirror
	Polarization analyzer: Out
	Illuminators: Of

The results are depicted in Fig. 20 and show Raman shift ( $\text{cm}^{-1}$ ) peaks at: positions including, but not limited to, any two, any three, any four, any five or all six of the peaks: 1617.66, 1448.22, 1374.09, 976.28, 801.60, or any combinations of 2, 3, 4, 5 or more peaks.

#### Celecoxib-Potassium Salt (MO-116-49A) Data (PXRD)

A small amount of collected sample was placed in a 0.3mm glass PXRD tube. The tube was placed in Rigaku D/Max Rapid PXRD set to Cu; 46kV/40mA; Collimeter:0.3; Omega-axis oscillation, Pos(deg) 0-5, speed 1; Phi-axis spin, Pos 360, Speed 2; Collection time was equal to 15 minutes. The PXRD pattern has characteristic peaks as shown in Fig. 21. Peaks can be seen at 2-theta angles including, but not limited to, 4.03, 12.23, 15.35, and 19.79. The crystal can be characterized by any one, any two, any three, or all four, of the above angles or any one or combination of 2-theta angles of Fig. 21.

#### Example 10

##### Celecoxib-Potassium Salt: Preparation Method MO-116-55D

An alternative method of preparing a celecoxib-potassium salt of the instant invention was performed. 100mg of celecoxib (commercially available) was dissolved in 2.2mL toluene and 0.1mL methanol in a vial with a Teflon® coated silicon rubber septum cap. The solution was warmed gently during dissolution with occasional swirling until all solids were dissolved. 1.03 equivalents of KOH (Potassium Hydroxide – Spectrum, Cat# P0180, Lot#PN0690) using a 3M KOH(aq) solution were added to the solution. After the resulting phase separation, the bottom phase was removed and was

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dried by flowing dry nitrogen over the solution for 1 day through stainless steel needles inserted into the septum cap.

Analysis was performed. Characterization of the product was achieved via TGA (Fig. 22), Raman spectroscopy (Fig. 23) and PXRD (Fig. 24).

#### Celecoxib-Potassium Salt (MO-116-55D) Data (TGA)

5.4470 mg of collected sample was placed into a platinum TGA pan. The pan was placed in TA Instruments Q500 TGA and heated 10°C/min to 90°C, held for 10 minutes, ramped 10°C/min to 300°C, and held for 10 minutes with 40ml/min nitrogen purge gas. The results are depicted in Fig. 22 and show a weight loss of about 4.9wt% from 25 degrees C to 200 degrees C and about 2.9wt% at a shoulder from about 70 degrees C to 200 degrees C. Initial weight loss before the shoulder is most likely to the evaporation of methanol. The weight loss after the shoulder is most likely due to excess water.

#### Celecoxib-Potassium Salt (MO-116-55D) Data (Raman)

A small quantity of collected sample was placed on a glass slide and mounted in the Thermo Nicolet Almega Dispersive Raman. The sample capture was set to 6 background scans and 12 sample collection scans. The parameters of the spectrometer were as follows:

DATA COLLECTION INFORMATION	SPECTROMETER DESCRIPTION
Exposure time: 2.00 sec	Spectrometer: Visible Raman Microscope
Number of exposures: 12	Laser: 785 nm
Number of background exposures: 6	Laser power level: 100%
	Laser polarization: Parallel
	Grating: 360 lines/mm
	Spectrograph aperture: 100 µm slit
	Sample position: Microscope
	Camera temperature: -50 C
	CCD rows binned: 89-150
	CCD binning: On chip
	RIM position: Mirror
	Polarization analyzer: Out.
	Illuminators: Of

The results are depicted in Fig. 23 and show Raman shift ( $\text{cm}^{-1}$ ) peaks at positions including, but not limited to, any two, any three, any four, any five or all six of the peaks 1615.51, 1446.09, 1374.28, 973.01, 798.86, 739.82, or any combinations of 2, 3, 4, 5, 6 or more peaks of Fig. 23.

#### Celecoxib-Potassium Salt (MO-116-55D) Data (PXRD)

A small amount of collected sample was placed in a 0.3 mm glass PXRD tube. The tube was placed into a Rigaku D/Max Rapid PXRD set to Cu; 46kV/40mA; Collimeter:0.3; Omega-axis oscillation, Pos(deg) 0-5, speed 1; Phi-axis spin, Pos 360, Speed 2; Collection time was equal to 15 minutes. The results are depicted in Fig. 24.

#### Example 11

##### Celecoxib-Calcium Salt: Preparation Method MO-116-62A

100mg of celecoxib (commercially available) was dissolved in a 1M NaOH methanol solution at a 1:1 ratio of NaOH:Celecoxib in a vial and heated gently with occasional swirling until all solids were dissolved. 3M  $\text{CaCl}_2$  in methanol was added to achieve a ratio of 1.5:1  $\text{Ca}^{2+}$  to Celecoxib. The precipitate was filtered with a centrifuge tube filter (Corning Inc. Costar (0.22 micron) #8169) in an Eppendorf Centrifuge (5415D) set at 12000 rpm for 5 minutes. The upper section of the Eppendorf tube containing the solids was placed into a vial with a rubber septum cap. The powder was dried overnight by flowing dry nitrogen into the vial through stainless steel needles inserted in the septum cap.

Analysis was performed. Characterization of the product was achieved via TGA (Fig. 25), Raman spectroscopy (Fig. 26) and PXRD (Fig. 27).

#### Celecoxib-Calcium Salt (MO-116-62A) Data (TGA)

3.4140 mg of collected sample was placed into a platinum TGA pan. The pan was placed in TA Instruments Q500 TGA and heated  $10^\circ\text{C}/\text{min}$  to  $90^\circ\text{C}$ , held for 10 minutes, ramped  $10^\circ\text{C}/\text{min}$  to  $300^\circ\text{C}$ , and held for 10 minutes with 40ml/min nitrogen purge gas. Results (Fig. 25) show a weight loss of about 4.2% between 25 and 200 degrees C and about 3.2% between 70 and 200 degrees C. Initial weight loss below 70 degrees C is due to unbound solvent. The shoulder seen after 70 degrees C is due to the loss of more closely bound methanol and represents 0.45 equivalents of methanol.

#### Celecoxib-Calcium Salt (MO-116-62A) Data (Raman)

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A small quantity of collected sample was placed on a glass slide and mounted in the Thermo Nicolet Omega Dispersive Raman. The sample capture was set to 6 background scans and 12 sample collection scans.

DATA COLLECTION INFORMATION	SPECTROMETER DESCRIPTION
Exposure time: 2.00 sec	Spectrometer: Visible Raman Microscope
Number of exposures: 12	Laser: 785 nm
Number of background exposures: 6	Laser power level: 100%
	Laser polarization: Parallel
	Grating: 360 lines/mm
	Spectrograph aperture: 100 $\mu$ m slit
	Sample position: Microscope
	Camera temperature: -50 C
	CCD rows binned: 89-150
	CCD binning: On chip
	RIM position: Mirror
	Polarization analyzer: Out
	Illuminators: Of

Raman shift ( $\text{cm}^{-1}$ ) peaks were observed at positions including, but not limited to, any one, any two, any three, any four, any five, and six or all seven of the peaks 16.16.99, 1598.42, 1450.05, 1376.57, 973.10, 800.62, 642.20, or any combinations of 2, 3, 4, 5, 6, 7 or more peaks of Fig. 26.

#### Celecoxib-Calcium Salt (MO-116-62A) Data (PXRD)

A small amount of collected sample was placed into a 0.3 mm glass PXRD tube. The tube was placed in Rigaku D/Max Rapid PXRD set to Cu; 46kV/40mA; Collimeter:0.3; Omega-axis oscillation, Pos(deg) 0-5, speed 1; Phi-axis spin, Pos 360, Speed 2; Collection time was equal to 15 minutes. An intense peak was observed at 2-theta angle of 31.67 and lesser peaks at 7.82, 9.27, 20.56, and 27.35. Any one or combination of 2, 3, 4, or 5 of the preceding peaks can be used to characterize the salt, as well as, any 1, 2, 3, 4, 5, 6, or more peaks of Fig. 27.

#### Example 12

##### Comparative Analysis of Neutral Celecoxib

To aid in the analysis of some of the data retrieved, commercially available celecoxib was subjected to the same analytical techniques of particle-induced X-ray diffraction (PXRD) and Raman spectroscopy. The results were used as a comparison for the salts of the instant invention.

**Comparison Data: Celecoxib (PXRD)**

A small amount of commercially available celecoxib was placed in a 0.3 mm glass PXRD tube. The tube was placed in Rigaku D/Max Rapid PXRD set to Cu; 46kV/40mA; Collimeter:0.3; Omega-axis oscillation, Pos(deg) 0-5, speed 1; Phi-axis spin, Pos 360, Speed 2; Collection time was equal to 15 minutes. The results are depicted in Fig. 28.

**Comparison Data: Celecoxib (Raman)**

A small quantity of commercially available celecoxib was placed on a glass slide and mounted in the Thermo Nicolet Almega Dispersive Raman. The sample capture was set to 6 background scans and 12 sample collection. The parameters were as follows:

DATA COLLECTION INFORMATION	SPECTROMETER DESCRIPTION
Exposure time: 2.00 sec	Spectrometer: Visible Raman Microscope
Number of exposures: 12	Laser: 785 nm
Number of background exposures: 6	Laser power level: 100%
	Laser polarization: Parallel
	Grating: 360 lines/mm
	Spectrograph aperture: 100 µm slit
	Sample position: Microscope
	Camera temperature: -50 C
	CCD rows binned: 89-150
	CCD binning: On chip
	RIM position: Mirror
	Polarization analyzer: Out
	Illuminators: Of

The results are depicted in Fig. 29.

**Example 13**

Solid-state formulations based on selected Pluronic excipients in combination with hydroxypropylcellulose (HPC) and the crystalline celecoxib sodium hydrate salt, prepared using traditional mortar and pestle technique, showed enhanced dissolution of the celecoxib salt in simulated gastric fluid.

This example demonstrates that related solid-state formulations enhance the dissolution and retard the recrystallization of celecoxib salts as compared to the celecoxib freeacid compound. The processes used to identify and test the preferred excipients in these examples are two-fold: (1) A "Crystal Retardation Assay" was used to identify excipients that supersaturate celecoxib in solution; and (2) In-vitro dissolution studies were performed on selected excipients to verify the "Crystal Retardation Assay" results.

#### Example 14

##### Crystal retardation Assay

##### Crystal retardation Assay - Method

1. 58 excipients according to Table 1 were prepared at a concentration of 2 mg/ml (0.2% by weight) in simulated gastric fluid having 200 mM hydrochloric acid and dispensed in quadruplicate in 96-well plates at a volume of 150 ul. Two controls were used: (a) Simulated gastric fluid lacking excipients; and (b) Simulated gastric fluid containing 2 mg/ml Vitamin E TPGS and 2 mg/ml HPC. The latter control was chosen because of prior indication that this excipient combination provides enhanced dissolution of celecoxib sodium hydrate. Simulated gastric fluid was prepared by adding 2 g/L sodium chloride and 1 g/L Triton X-100 to DI H2O. 200 mM hydrochloric acid was added to adjust and buffer the pH.

Table 1.

Excipients use in Recrystallization Retardation Assay		
2 Ethoxyethanol	Polyethyleneglycol Monooleate (Mapeg 400-MO)	Pluronic P123
Alkamus 719		
Alkamus EL 620	Polyethyleneglycol 300	Pluronic P85
Alkamus EL 719	Pluronic 17R2	Poloxamer 188
Benzyl Alcohol	Pluronic F108	Poloxamer 338
Cremophor EL	Pluronic F127	Polypropyl 52
Cremophor RH40	Pluronic F38	Polysorbate 40
Crillet 1 HP	Pluronic F68	Polysorbate 80
Crovol A-70	Pluronic F77	Propylene Glycol
Ethospense G-26	Pluronic F87	Polyvinylpyrrolidone 10K
Ethylene Glycol	Pluronic F88	Polyvinylpyrrolidone 360K
Glycerin	Pluronic F98	Polyvinylpyrrolidone 55K
HEC 250K		Saccharin
Hydroxypropylcellulose (HPC)	Pluronic L31	Sodium lauryl sulphate
Isopropanolamine	Pluronic L43	Tagat 02
Myrj 52	Pluronic L44	Transcutol P
Polyethyleneglycol 1000	Pluronic L92	Triacetin



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Polyethyleneglycol 200	Pluronic P103	Triethanol amine
Polyethyleneglycol 400	Pluronic P104	Vitamin E TPGS
Polyethyleneglycol 600	Pluronic P105	Vitamin E TPGS & HPC

2. The 96-well plates were sealed, and incubated to a temperature of 40°C for 20 minutes. After incubation, the plate seals were removed.
3. Celecoxib, pre-dissolved in potassium hydroxide to a concentration of 5.5 mg/ml, was dispensed in 15 ul aliquots into each well and immediately mixed. This gave a final celecoxib concentration of 0.5 ml/ml in each well. The final excipient concentration was 1.8 mg/ml.
4. A nephelometer (*Nephelostar Galaxy, BMG Technologies, Durham, NC*), with a chamber preheated to 37°C, was used to analyze the ability of the excipients to retard the crystallization of supersaturated celecoxib. The assay plate containing celecoxib and excipients was sealed using an optically clear seal and placed into the nephelometer instrument. The nephelometer recorded changes in solution turbidity over a 1 hour time period. Solutions that showed signs of increasing turbidity over a baseline indicated that celecoxib had precipitated out solution.

#### Crystal retardation Assay - Results:

Fig. 30 shows crystal retardation time for celecoxib as a function of excipient in simulated gastric fluid (SGF). Final concentration of celecoxib was 0.5 mg/ml. Black bars indicate crystal retardation time that may be greater than 60 min. Excipients listed in Table I, but excluded from Fig. 30 did not show any appreciable crystal retardation time (i.e., greater than 1.5 min). Nineteen of 58 excipients were found to retard recrystallization of celecoxib. Interestingly, in contrast to the dissolution assay, Vitamin E TPGS alone had a longer retardation time than in combination with HPC; and (3) HPC did not show any retardation time.

Importantly, formulations that increase the solubility of a drug will not necessarily increase the dissolution. For example, according to PCT application WO 01/78724, the solubility of celecoxib free acid in Transcutol P is 350 mg/g. It was found that in contrast to enhancing solubility, Transcutol P does not enhance dissolution of the free acid. Transcutol P does extend the time to T<sub>max</sub> and increases the time the concentration of celecoxib is above ½ T<sub>max</sub> when used in combination with a recrystallization retardant and enhancer. It was further found that dissolution of a salt form is far superior to the dissolution of composition comprising the free acid.

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The presence of six Pluronic (poloxamer) excipients among successful crystal retardants prompted further study of these compounds. Pluronics are ethylene oxide - propylene oxide block copolymers, whose properties can be significantly altered (i.e., melting point, cloud point, molecular weight, HLB number, surface tension, interfacial tension, etc.) by adjusting the ratio of copolymer blocks. Further examination of these properties showed that the surface tension of these copolymers at a 0.1% concentration in water correlates with the ability to retard the crystallization of celecoxib. Pluronic excipients having low interfacial tension (i.e., less than 10 dyne/cm) or having a surface tension less than 42 dyne/cm were more effective at keeping celecoxib in solution than Pluronic excipients having high interfacial tension or surface tension. This observation is illustrated in Fig. 31, along with interfacial data for Pluronics that were not tested. Based on this correlation, the supersaturation properties of these additional Pluronics also correlate with interfacial tension.

Fig. 31 shows interfacial tension of selected Pluronic excipients in water. Pluronic excipients having low interfacial tension correlate with excipients that retard crystallization of celecoxib in simulated gastric fluid. An interfacial tension threshold for crystal retardation was loosely defined as greater than 9 dyne/cm. Excipient concentration in the assay was 0.18%; celecoxib concentration was 0.5mg/ml. Pluronic is trademark of BASF. Interfacial data obtained from BASF at 0.1% concentration in water versus mineral oil at 25°C.

#### Example 15

##### In Vitro Dissolution Studies of Pluronic Excipients

##### In Vitro Dissolution Studies of Pluronic Excipients - Method

###### 1. Celecoxib Preparation

- a. Fresh celecoxib sodium salt hydrate was prepared and analyzed to be approximately 90% freeacid vs. sodium content.
- b. The celecoxib salt was ground using mortar and pestle until fine powder was formed. The fine powder was sieved using a 105 um pore size mesh and stored in a 20 ml scintillation vial at room temperature.

###### 2. Formulation Preparation

- a. Fresh Pluronic excipient was dispensed into a mortar. If initially a solid at room temperature, the Pluronic was ground until a smooth powder was formed.

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- b. If HPC was to be added, it was dispensed after the Pluronic excipient. The HPC was combined with the Pluronic and the two were ground together using a pestle and mixed with a spatula for 1 minute.
- c. 105 um sieved celecoxib salt was added to mortar and the mixture was ground and mixed for several minutes.
- d. If needed, a liquid excipient such as Poloxamer 124, Peg 200, or Peg 400 was added to the mortar as a granulating fluid-like liquid to form an intimate contact between drug and excipient. The mixture was ground and mixed until a uniform consistency was observed in the solid-state mixture.

### 3. Dissolution Assay

- a. A water bath was set up at 37°C.
- b. Simulated gastric fluid in the fasted state (SGF) was prepared at pH 1.7 and diluted five times with deionized water. The final pH was approximately 2.4. The simulated gastric fluid was diluted five times to simulate the effect of drinking a glass of water with the medication. The SGF was pre-heated to 37°C.
- c. The formulation was placed in a 20 ml scintillation vial.
- d. A 10 mm x 3 mm stir bar was added.
- e. Diluted SGF was added to the formulation. The volume added was set to satisfy a 2 mg/ml dose of celecoxib free acid.
- f. The vial was placed in the water bath and allowed to stir.
- g. At each time point, 0.9 ml of solution was extracted and filtered through a 0.2 um polyvinylflouridine filter. The first 2/3 of filtrate was discarded as waste and the last 1/3 was collected into an eppendorf tube. 0.1 ml of the collected filtrate was immediately transferred to an autosampler vial and diluted ten times with 0.9 ml of methanol. The autosampler vials were crimp sealed and submitted for content analysis using high performance liquid chromatography with ultra-violet detection.
- h.

#### In Vitro Dissolution Studies of Pluronic Excipients - Results:

- 1. Dissolution of two Pluronic excipients that had low interfacial tension: Pluronic P123 and F127. Pluronic P123 was a paste at room temperature, and resulted in sticky formulation of celecoxib salt. Pluronic F127 was a solid at room temperature and formed a flowable powder

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solid-state mixture with the celecoxib salt. The dissolution result for these mixtures at equal weight concentrations of excipient to celecoxib freeacid content are shown in Figure 32.

Pluronic P123 gave enhanced dissolution of celecoxib salt, while Pluronic F127 did not. The poor performance of Pluronic F127 in enhancing celecoxib dissolution was due to the slow dissolution of the excipient. In contrast, Pluronic P123 was intimately bound with the celecoxib salt in a "sticky" waxy mass, which delayed the dissolution of celecoxib. This allowed the excipient to dissolve to a greater extent prior to the full dissolution of the celecoxib salt form.

2. Dissolution of celecoxib sodium hydrate was performed in the presence of HPC using Pluronic P123, Pluronic F127, and Pluronic F87; Pluronic F87 has a high interfacial tension value. Equal weight concentrations of Pluronic and HPC to celecoxib free acid content were used in the formulations. The Pluronic P123 formulation was sticky due to the pasty nature of the excipient. The Pluronic F127 and F87 formulation were flowable since these excipients are solids at room temperature. Dissolution data for these formulations are shown in Fig. 33. The data showed that addition of HPC in the Pluronic P123 formulation produced a widening of the dissolution profile. In the Pluronic F127 formulation, HPC enhanced the initial dissolution component of the profile (i.e. < 10 minutes). In contrast, no dissolution profile was observed in the Pluronic F87 formulation. Since Pluronic 87 has a high interfacial tension (17.4 dyne/cm), the resulting data supports the correlation of crystal retardants with interfacial tension. Since the Pluronic P123 formulation (i.e., sticky) showed a dissolution profile that was enhanced to a greater extent than the Pluronic F127 formulation (i.e., loose powder) in terms of time to recrystallization, it was hypothesized that the addition of an excipient that physically binds the components of the Pluronic F127 formulation will result in further dissolution enhancement.
3. Dissolution of celecoxib sodium hydrate using Pluronic F127 and HPC was performed using a granulated fluid-like liquid to bind the solid-state mixture. Three granulating fluid-like liquids were chosen: Peg 200, Peg 400, and Poloxamer 124. Equal weight ratios of celecoxib free acid content, Pluronic F127, and HPC were formulated with 40-45% celecoxib freeacid weight of granulating fluid. The effect of these formulations on dissolution is shown in Fig. 34. The granulating fluid-like liquids increased the dissolution of celecoxib, possibly by delaying the

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contact between the celecoxib salt and the dissolution media until Pluronic F127 had been dissolved to a significant extent.

4. Dissolution of celecoxib sodium hydrate was then measured from a compacted formulation containing Pluronic F127 and HPC excipients. Formulations containing equal weight ratios of celecoxib freeacid content, Pluronic F127, and HPC were mixed and compacted into 6 mm discs at 4900 psi. Dissolution results, shown in Fig. 35, indicated enhanced dissolution with onset retarded by approximately 15-20 minutes. The compaction process produced a similar effect on dissolution to that observed by the addition of a granulating fluid (see Fig. 34) with the addition of controlled release mechanism. The controlled release characteristic of the profile can be modulated by selecting HPC or HPMC with varying grades of viscosity and the addition of disintegrants into the compact. Compacts are attractive formulations due to their lower production cost and fewer processing steps.

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**Claims:**

1. A pharmaceutical composition comprising:

- (a) a salt form of a drug having low solubility in gastric fluid conditions;
- (b) a recrystallization retardant; and
- (c) a an optional enhancer;

wherein the composition retards recrystallization of the drug for at least 5 minutes in gastric fluid conditions.

2. The pharmaceutical composition according to claim 1, wherein the recrystallization retardant is a surfactant.

3. The pharmaceutical composition according to claim 2, wherein the surfactant has an interfacial tension of less than 10 dyne/cm or a surface tension of less then 42 dyne/cm.

4. The pharmaceutical composition according to claim 3, wherein the surfactant is a poloxamer.

5. The pharmaceutical composition according to claim 4, wherein the poloxamer has an interfacial tension of less than 10 dyne/cm or surface tension less then 42 dyne/cm.

6. The pharmaceutical composition according to claim 2, wherein the composition comprises an enhancer.

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7. The pharmaceutical composition according to claim 3, wherein the composition comprises a cellulose ester as an enhancer.
8. The pharmaceutical composition according to claim 4, wherein the composition comprises HPC or HPMC as an enhancer.
9. The pharmaceutical composition according to claim 5, wherein the composition comprises HPC as an enhancer.
10. The composition according to claim 7, wherein recrystallization is retarded for at least 10 minutes.
11. The composition according to claim 10, wherein recrystallization is retarded for at least 15 minutes.
12. The composition according to claim 10, wherein recrystallization is retarded for at least 20 minutes.
13. The composition according to claim 10, wherein recrystallization is retarded for at least 25 minutes.
14. The composition according to claim 10, wherein recrystallization is retarded for at least 30 minutes.
15. The composition according to claim 10, wherein recrystallization is retarded for at least 35 minutes.
16. The composition according to claim 10, wherein recrystallization is retarded for at least 40 minutes.
17. The composition according to claim 10, wherein recrystallization is retarded for at least 45 minutes.

18. The composition according to claim 10, wherein recrystallization is retarded for at least 60 minutes.
19. The pharmaceutical composition according to claim 1, wherein the drug comprises a sulfonamide drug.
20. The pharmaceutical composition according to claim 19, wherein the sulfonamide drug is a benzene sulfonamide.
21. The pharmaceutical composition according to claim 20, wherein the benzene sulfonamide comprises celecoxib, deracoxib, valdecoxib, rofecoxib or eturicoxib.
22. The pharmaceutical composition according to claim 20, wherein the benzene sulfonamide is in the form of an alkali metal or alkaline earth metal salt.
23. The pharmaceutical composition according to claim 1, wherein the aqueous solubility of the drug is not more than 0.1mg/ml when measured at 37°C.
24. The pharmaceutical composition according to claim 1, wherein the aqueous solubility of the drug is not more than 10mg/ml when measured at 37°C.
25. A process for producing a pharmaceutical composition for delivering a supersaturated concentration of a drug having low aqueous solubility, which process comprises intimately mixing together components (a) (b) and (c) of claim 1.
26. The process according to claim 25, wherein the drug comprises a sulfonamide drug.
27. A process according to claim 26, wherein the sulfonamide drug is a benzene sulfonamide.
28. The process according to claim 27, wherein wherein the benzene sulfonamide comprises celecoxib, deracoxib, valdecoxib, rofecoxib or eturicoxib.



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29. A process according to claim 28, wherein the benzene sulfonamide is in the form of an alkali metal or alkaline earth metal salt.
30. The process according to claim 25, wherein the aqueous solubility of the drug is not more than 0.1mg/ml when measured at 37°C.
31. The process according to claim 25, wherein the aqueous solubility of the drug is not more than 10mg/ml when measured at 37°C.
32. The pharmaceutical composition according to claim 1, wherein the salt is an alkali metal or alkaline earth metal salt.
33. The pharmaceutical composition according to claim 32, wherein the metal is sodium, potassium, lithium, calcium or magnesium.
34. The pharmaceutical composition according to claim 33, wherein the salt is crystalline.
35. The pharmaceutical composition according to claim 1, wherein:
  - (a) the bioavailability of the composition orally administered is at least 70%;
  - (b) the bioavailability of the composition orally administered is at least 80%;
  - (c) the bioavailability of the composition orally administered is at least 85%;
  - (d) the bioavailability of the composition orally administered is at least 90%;
  - (e) the bioavailability of the composition orally administered is at least 95%;
  - (f) the C<sub>max</sub> is at least 2 fold greater than a neutral form in vivo or in an in vitro dissolution assay;
  - (g) the C<sub>max</sub> is at least 3 fold greater than a neutral form in vivo or in an in vitro dissolution assay;
  - (h) the C<sub>max</sub> is at least 4 fold greater than a neutral form in vivo or in an in vitro dissolution assay;
  - (i) the C<sub>max</sub> is at least 5 fold greater than a neutral form in vivo or in an in vitro dissolution assay;

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- (j) the C<sub>max</sub> is at least 10 fold greater than a neutral form in vivo or in an in vitro dissolution assay; the C<sub>max</sub> is at least 2 fold greater than a neutral form in vivo or in an in vitro dissolution assay;
- (k) the C<sub>max</sub> is at least 25 fold greater than a neutral form in vivo or in an in vitro dissolution assay;
- (l) the C<sub>max</sub> is at least 50 fold greater than a neutral form in vivo or in an in vitro dissolution assay;
- (m) the C<sub>max</sub> is at least 100 fold greater than a neutral form in vivo or in an in vitro dissolution assay;
- (n) the C<sub>max</sub> is at least 250 fold greater than a neutral form in vivo or in an in vitro dissolution assay;
- (o) the C<sub>max</sub> is at least 500 fold greater than a neutral form in vivo or in an in vitro dissolution assay;
- (p) the C<sub>max</sub> is at least 750 fold greater than a neutral form in vivo or in an in vitro dissolution assay;
- (q) the C<sub>max</sub> is at least 1000 fold greater than a neutral form in vivo or in an in vitro dissolution assay;
- (r) the bioavailability of the composition is at least 50% greater than a neutral form;
- (s) the bioavailability of the composition is at least 75% greater than a neutral form;
- (t) the bioavailability of the composition is at least 2 fold that of a neutral form;
- (u) the bioavailability of the composition is at least 3 fold that of a neutral form;
- (v) the bioavailability of the composition is at least 4 fold that of a neutral form;
- (w) the bioavailability of the composition is at least 5 fold that of a neutral form; or
- (x) the bioavailability of the composition is at least 10 fold that of a neutral form.

- 65 -

**ABSTRACT**

The invention relates to increasing the solubility, dissolution and bioavailability of a drug with low solubility in gastric fluids conditions by combining the drug with a recrystallization retardant and an optional enhancer.

FIG. 1

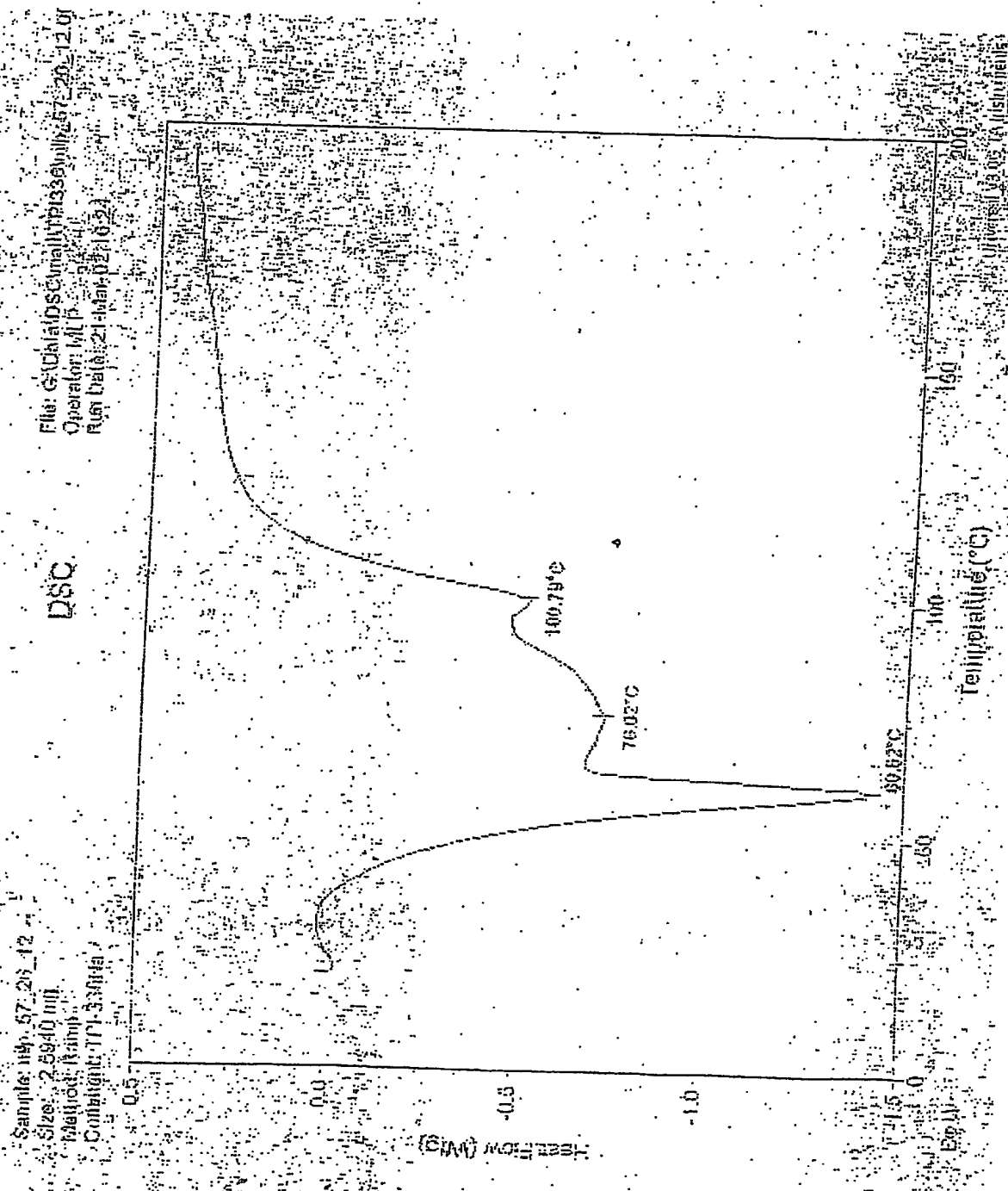


FIG. 2

File: G:\Data\TGA\Initial\TP13360.mpl  
Operator: ml.p  
Print Date: 21-Mar-02 16:29

TGA

Sample: mlp\_67\_26\_13  
Size: 2.1000 mm  
Method: 14-Res - Dynamic  
Comment: TP13360-1a

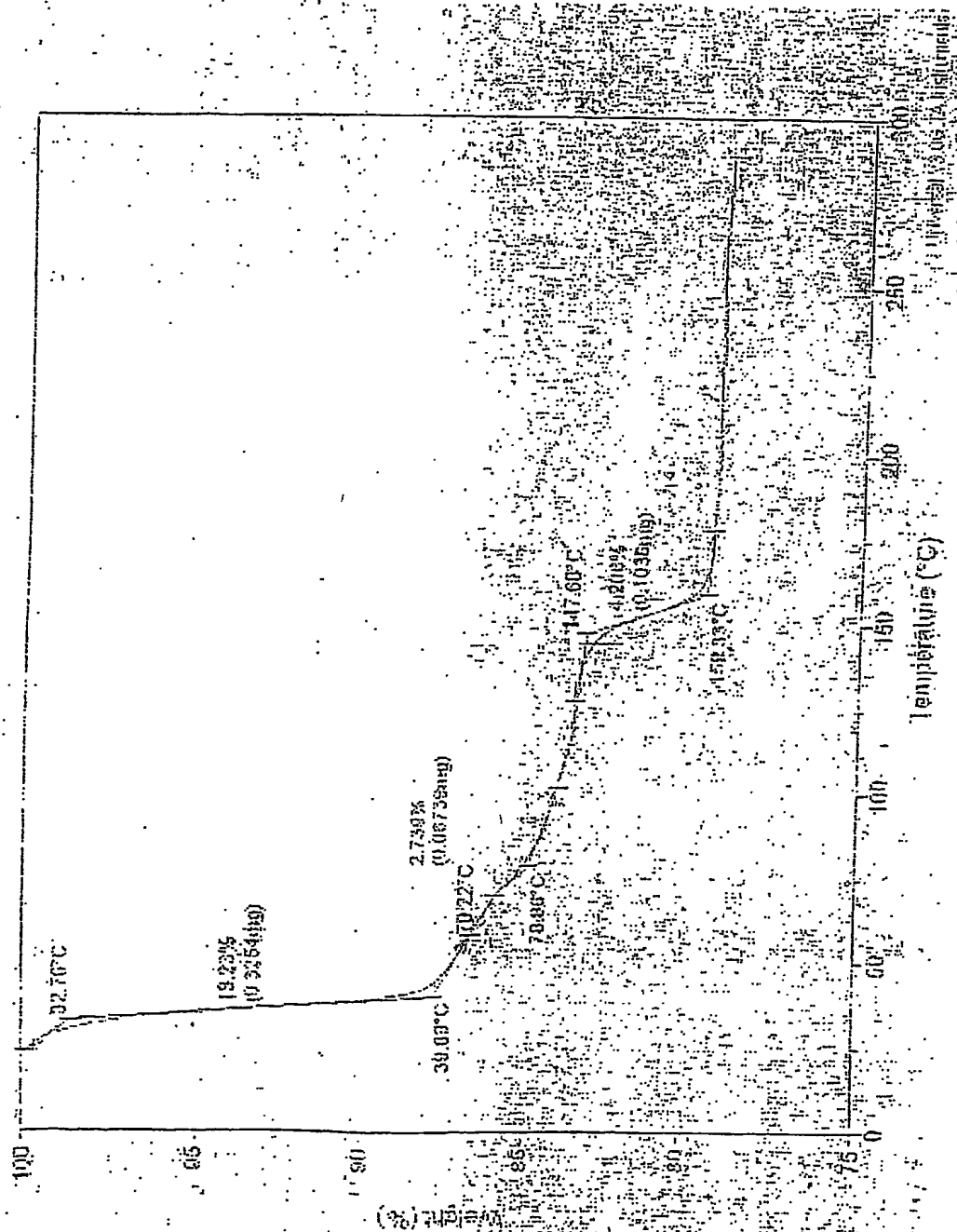
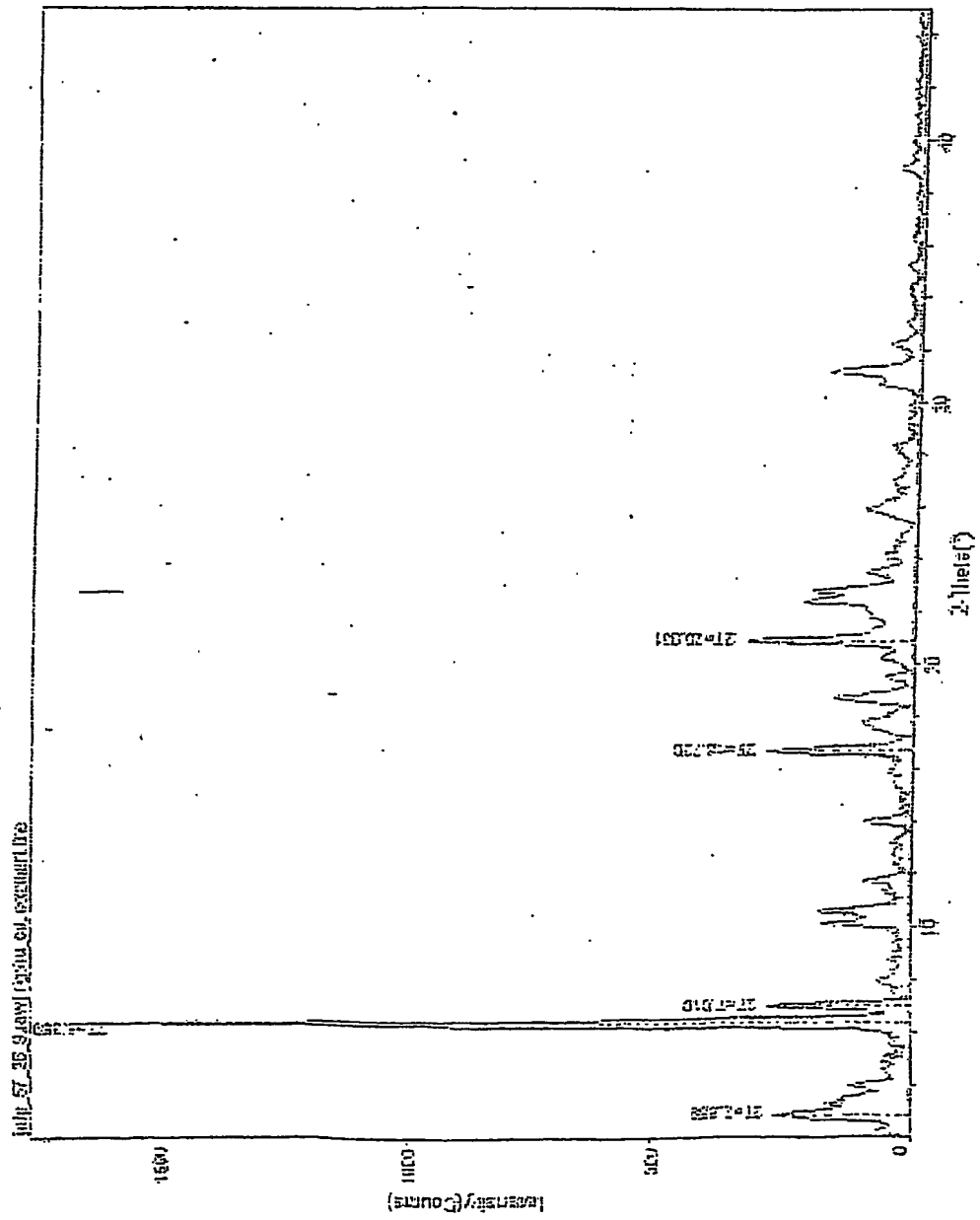


FIG. 3

TRANSFORM TRANSMUTATION, INC.



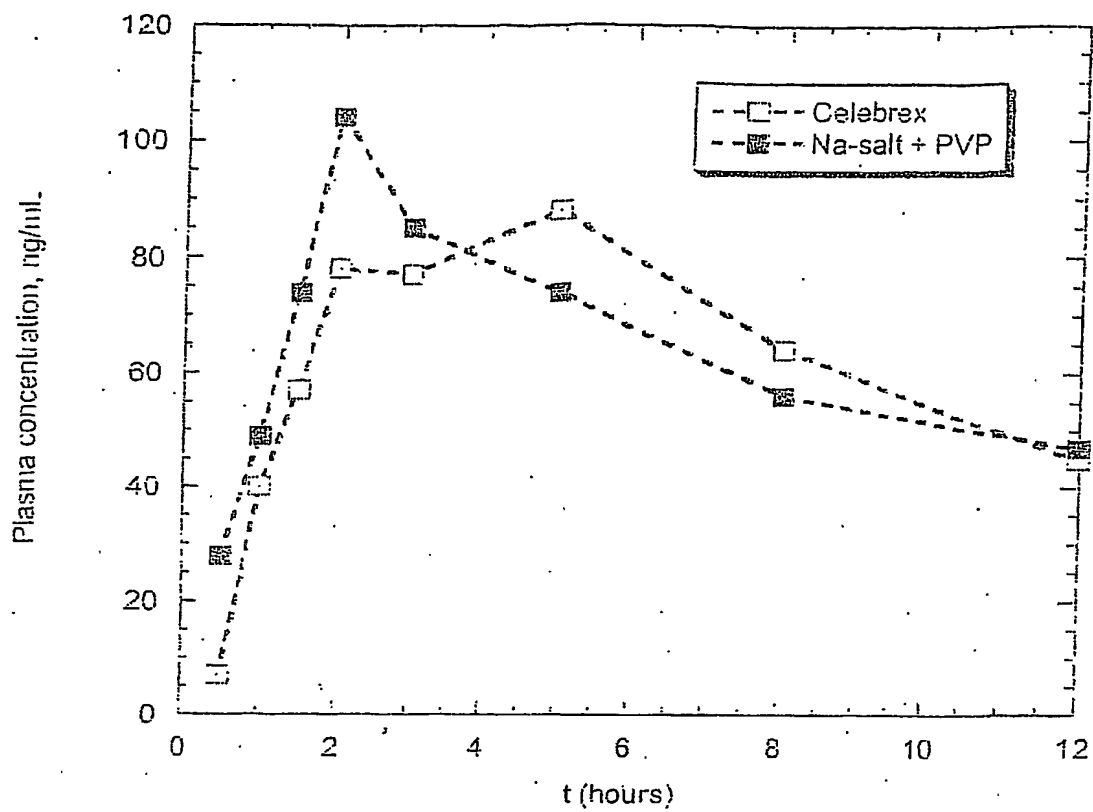


FIG. 4A

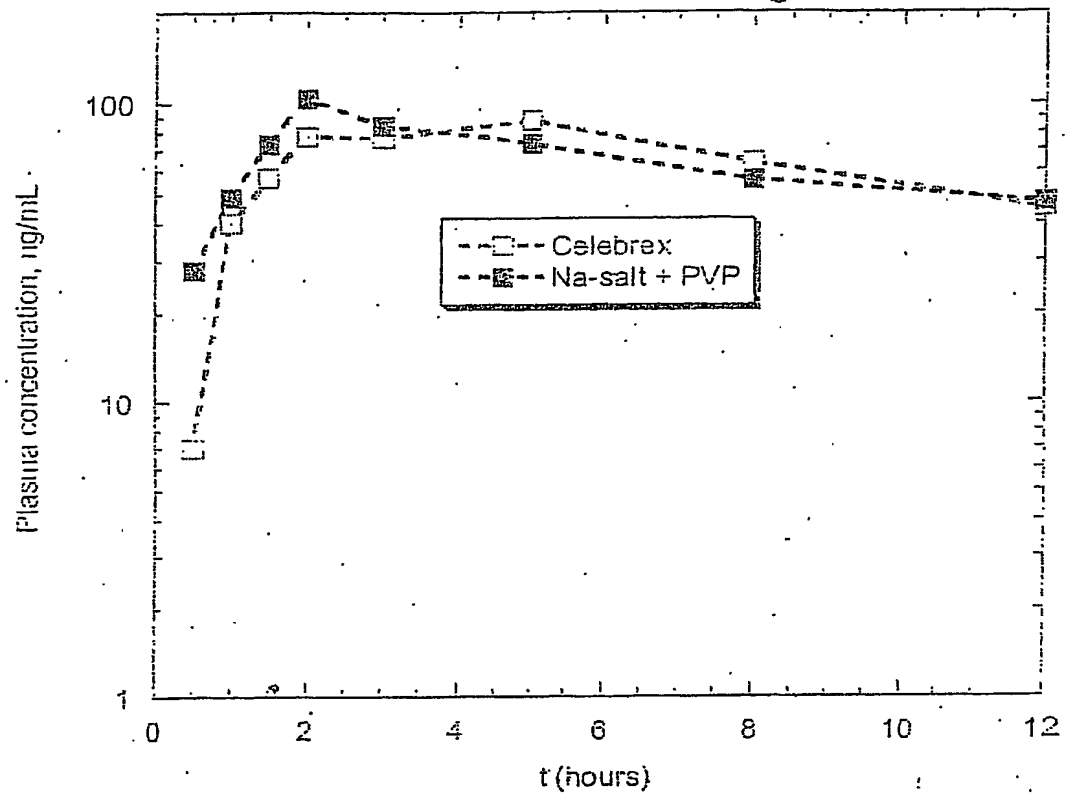


FIG. 4B



	Formulation	Dose Level (mg/kg)	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (min)	AUC <sub>(0-∞)</sub> (ng·hr/mL)	T <sub>1/2</sub> (hr)	Volume of Distribution at Steady State (mL/kg)	Clearance Rate (mL/hr·kg)	Bioavailability (%)
Mean	Celecoxib IV	1	718	NA	3808	8.21	2498	278	NA
SD		NA	91	NA	933	2.85	590	77	NA
Mean	Celecoxib PO	5.09	654	1.25	7663	9.3	NA	798	40.05
SD		0.050	199	0.88	3119	3.48	NA	317	15.45
Mean	Celecoxib Sodium PO	5.05	2142	0.75	16426	9.0	NA	323	85.80
SD		0.121	569	0.27	4150	2.71	NA	77	7.82

FIG. 5

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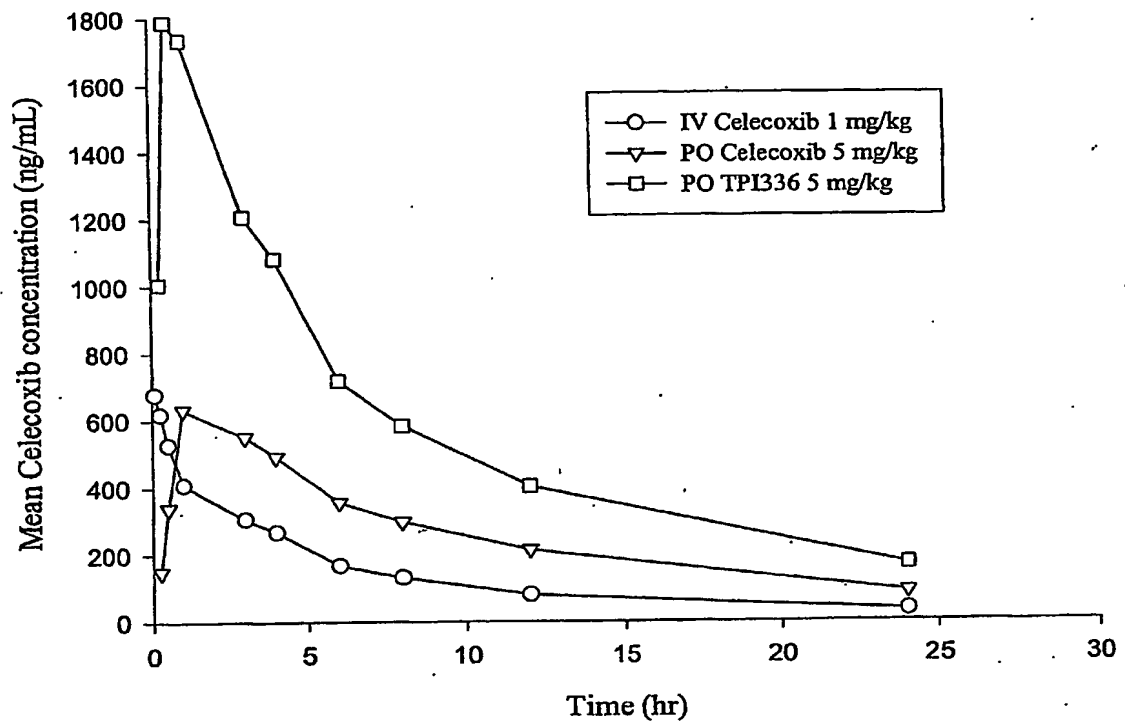
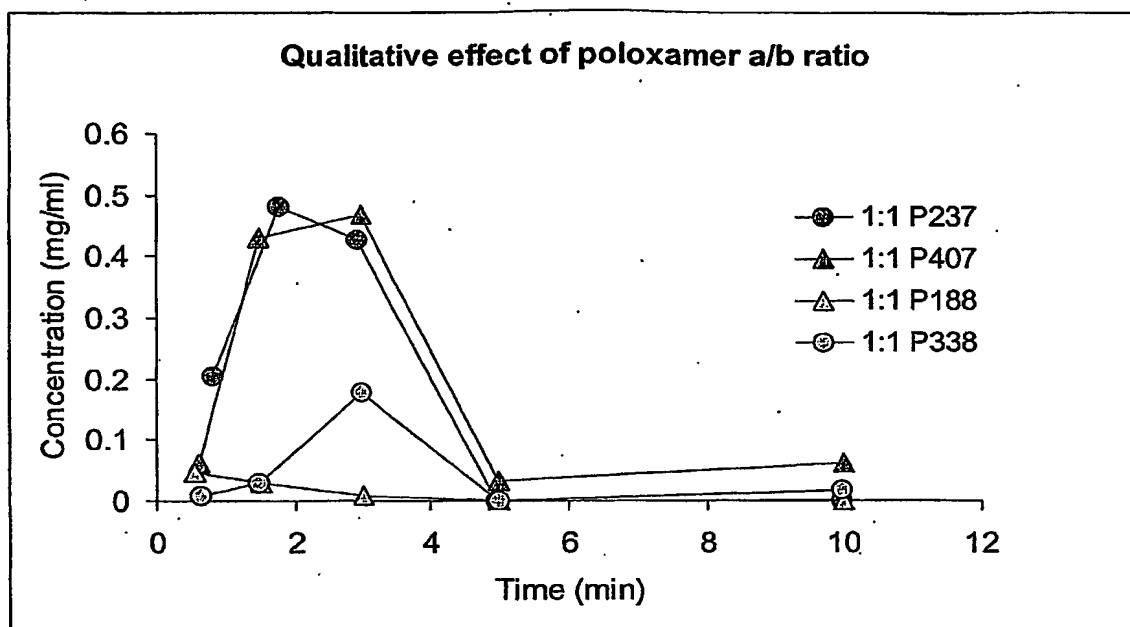


FIGURE 6



Poloxamer	Physical form	a	b	Average molecular weight	Percent a	Percent b	Ratio a/b
124	Liquid	12	20	2090-2360	0.38	0.63	0.60
188	Solid	80	27	7680-9510	0.75	0.25	2.96
		64	37	6840-8830	0.63	0.37	1.73
338	Solid	141	44	12 700-17 400	0.76	0.24	3.20
		101	56	9840-14 600	0.64	0.36	1.80

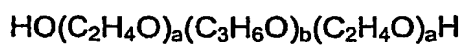


FIGURE 7

Effects of Celluloses on Dissolution of 1/1 Vitamin E TPGS/TPI-336-Na at Room Temperature

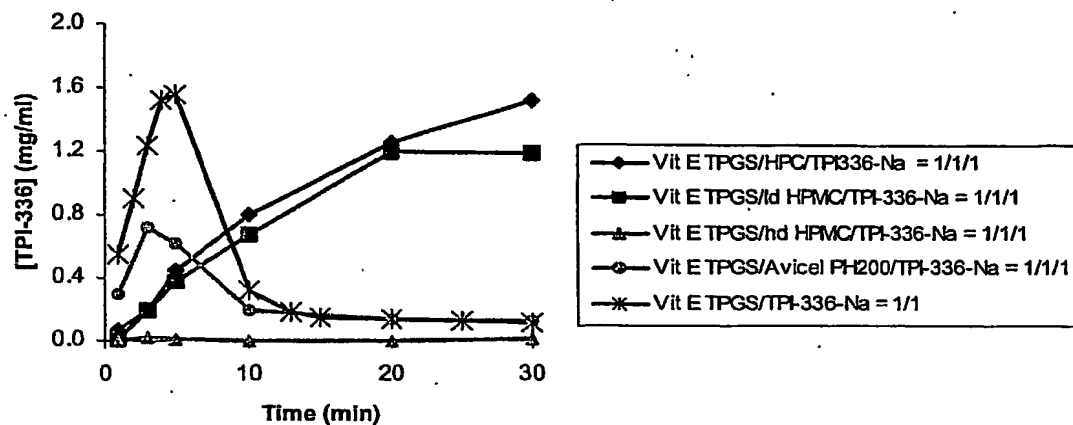


FIGURE 8

Dissolution Test at 37°C for Various Ratio of Vitamin E TPGS : HP-Cellulose : TPI336 Na

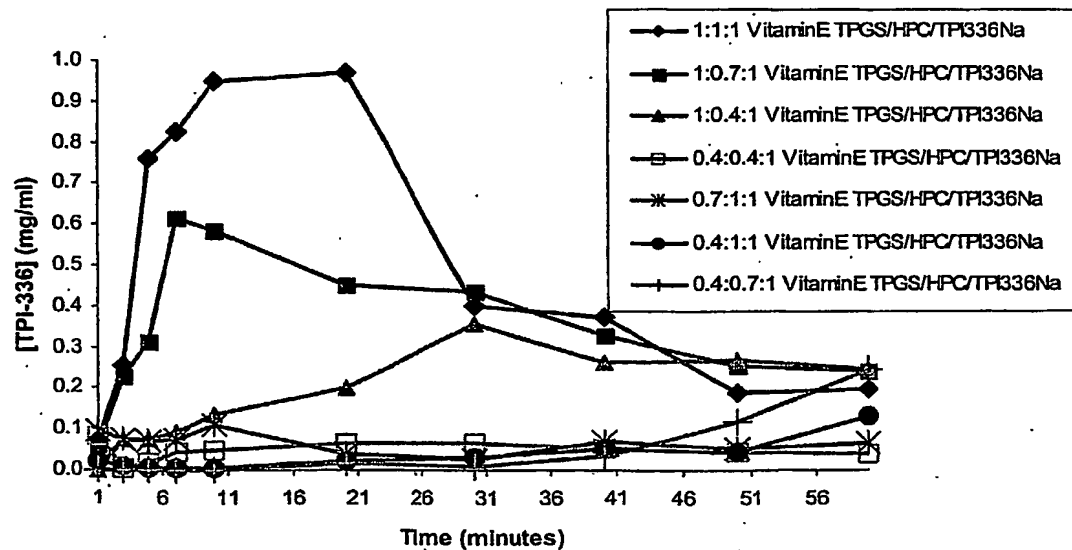


FIGURE 9

Dissolution profile of TPI-336-Na in SGF from solid mixtures with excipients at room temperature

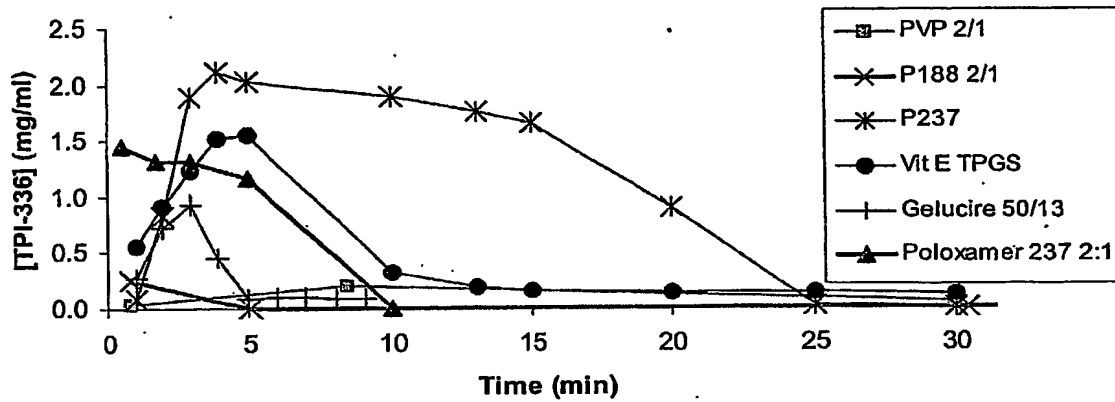


FIGURE 10

Effect of Avicel and Silica Gel on the dissolution of TPI336Na/Vit E TPGS/HPC mixtures in SGF at 37C

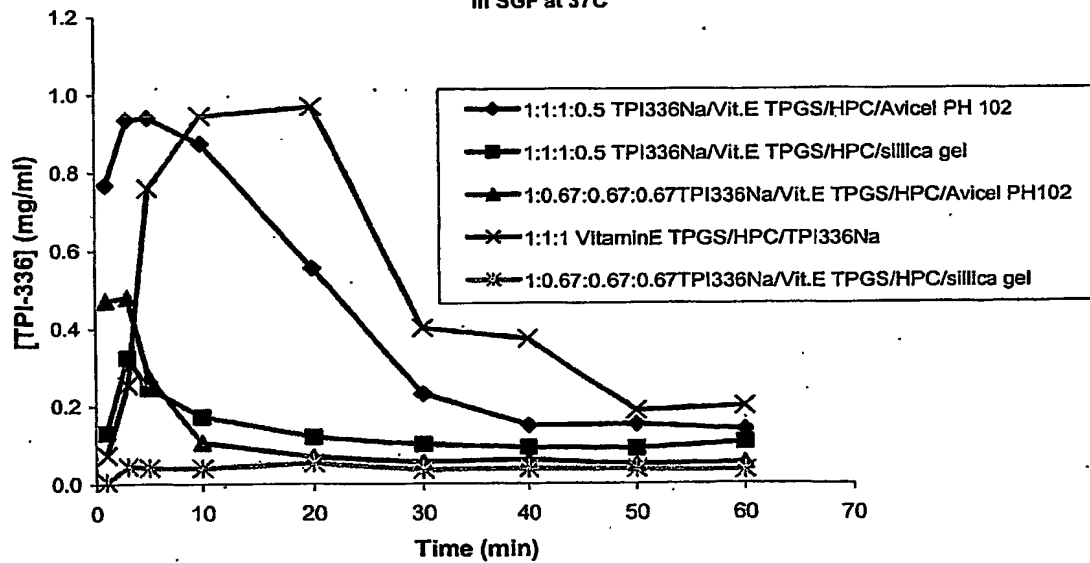


FIGURE 11

### Dissolution of TPI336Na at 37C in 5X diluted SGF

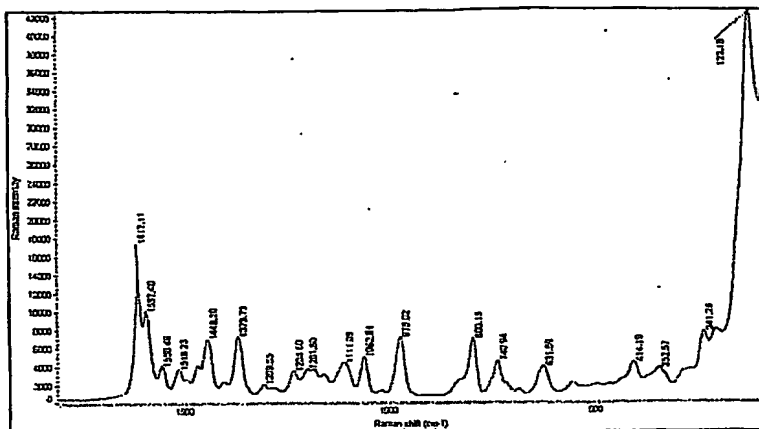


Figure 13B

Sample: mo-116-49b-celecoxib-LiOH  
Size: 1.5600 mg  
Method: Ramp

DSC

File: \\...mo-116-49b\_celecoxib-LiOH\_inN2.001  
Operator: MAO  
Run Date: 06-Dec-02 11:28

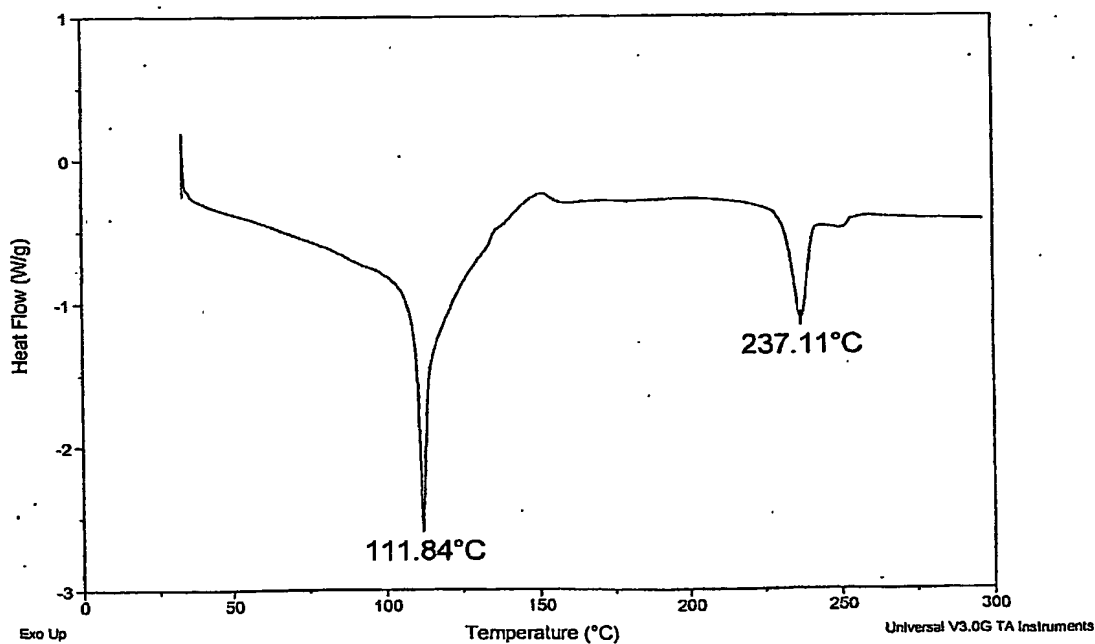


FIGURE 14

Sample: MO-116-49b\_celecoxib-LI  
Size: 8.2290 mg  
Method: Ramp

TGA

File: \\...MarkOlmo-116-49b\_celecoxib-LI001  
Operator: MAO  
Run Date: 08-Dec-02 16:36

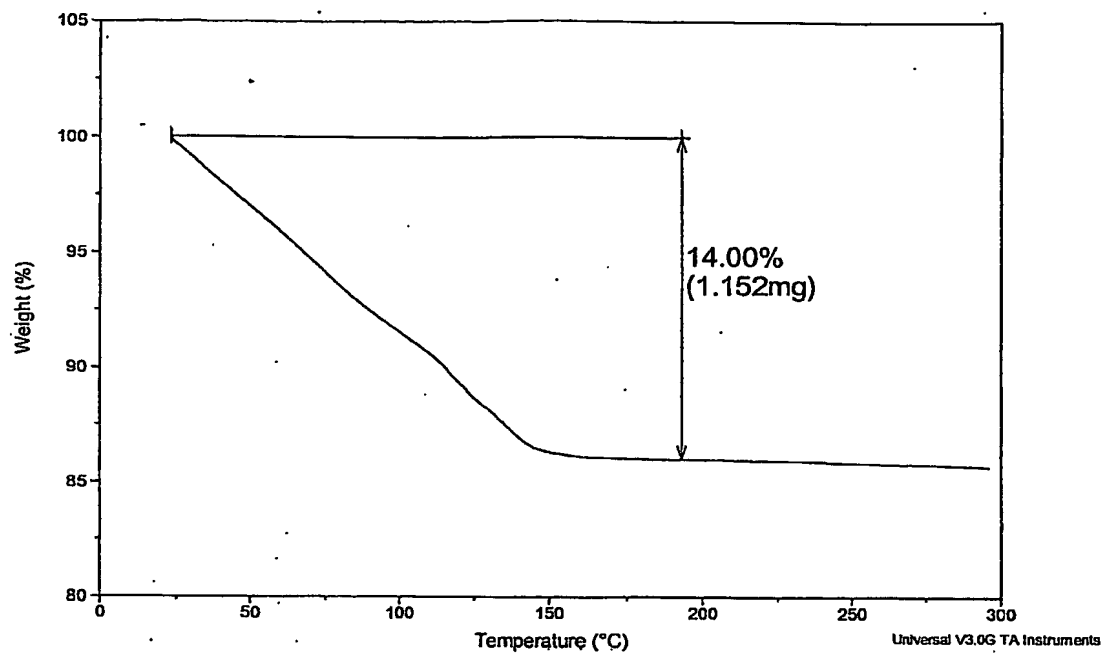


FIGURE 15



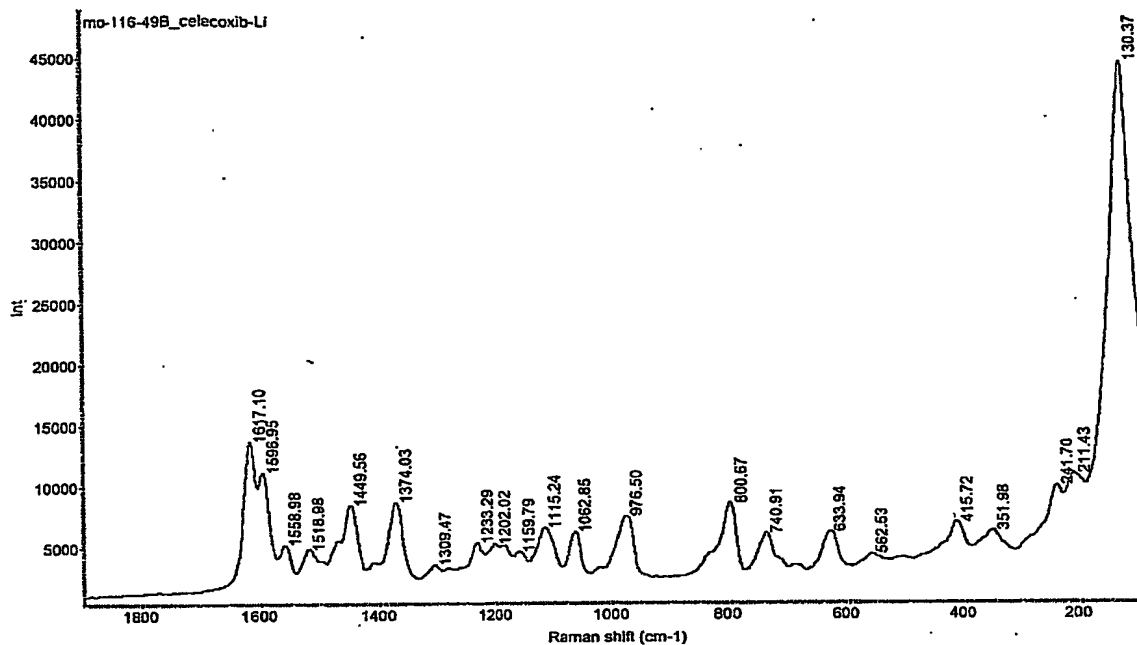


FIGURE 16

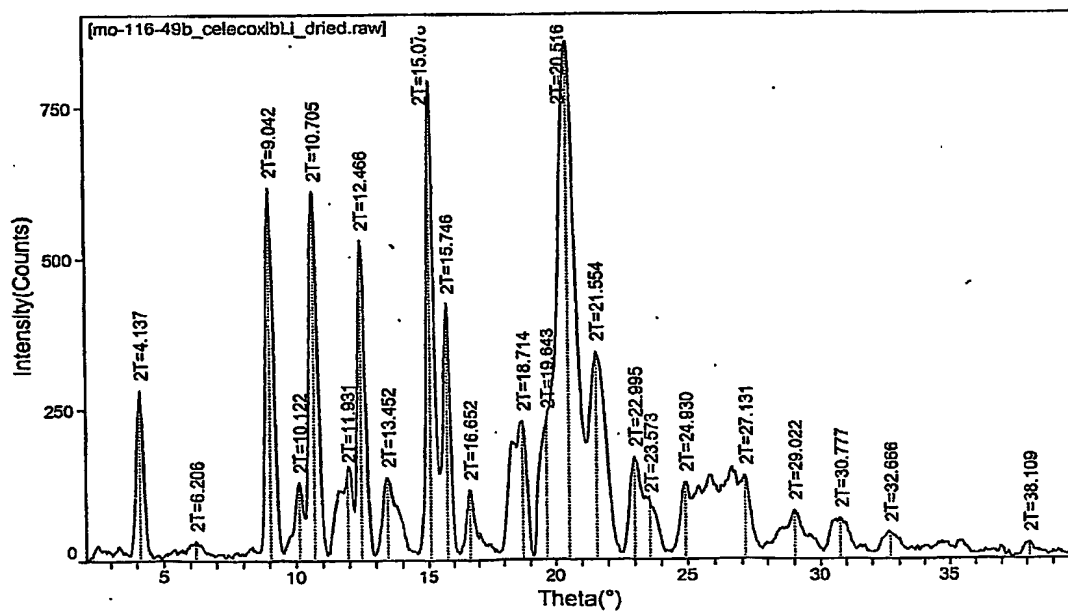


FIGURE 17

60456027.031803

Sample: mo-116-49a-celecoxib-KOH  
Size: 1.1190 mg  
Method: Ramp

DSC

File: \\...mo-116-49a\_celecoxib-KOH\_in2.001  
Operator: MAO  
Run Date: 08-Dec-02 10:55

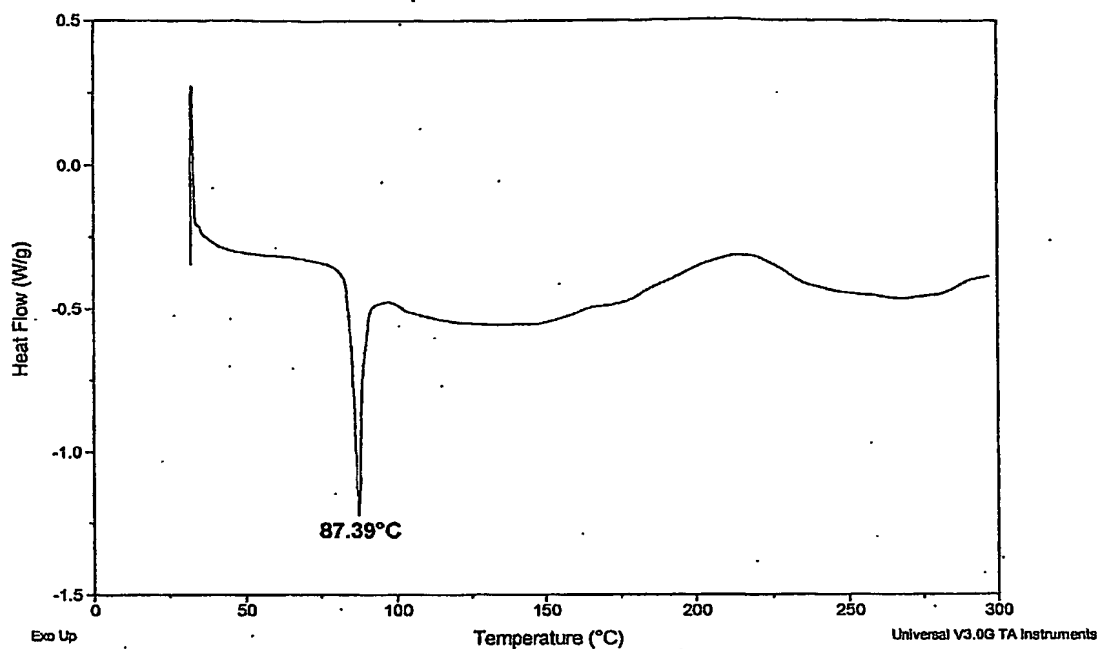


FIGURE 18

Sample: MO-116-49a\_celecoxib-K  
Size: 5.8890 mg  
Method: Stepwise Isothermal

TGA

File: \\...MarkOlmo-116-49a\_celecoxib-K.001  
Operator: MAO  
Run Date: 06-Dec-02 11:35

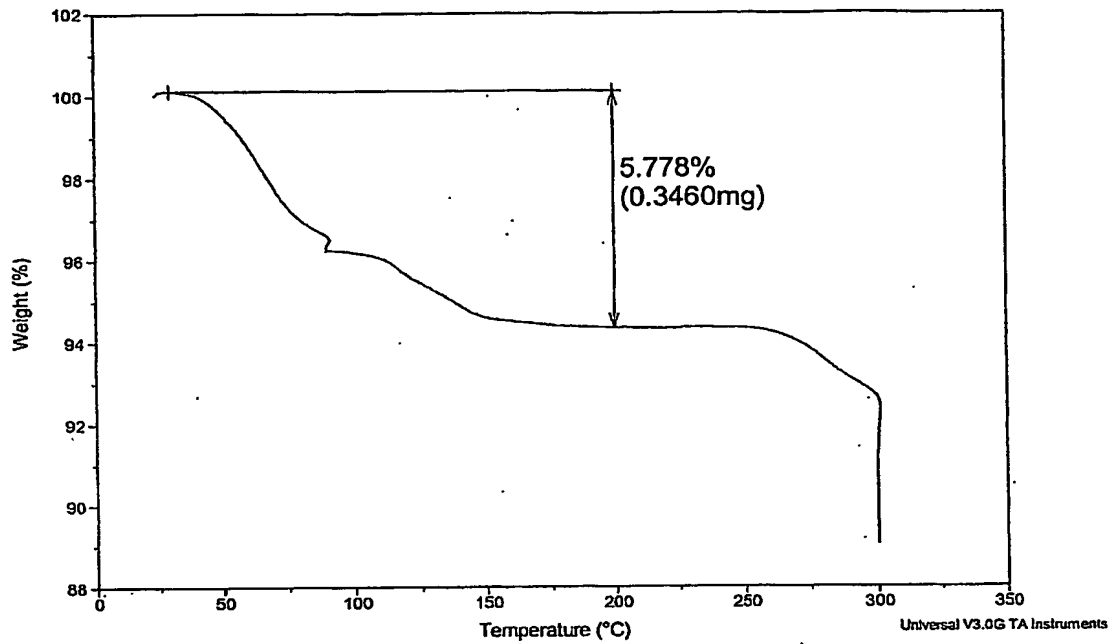


FIGURE 19

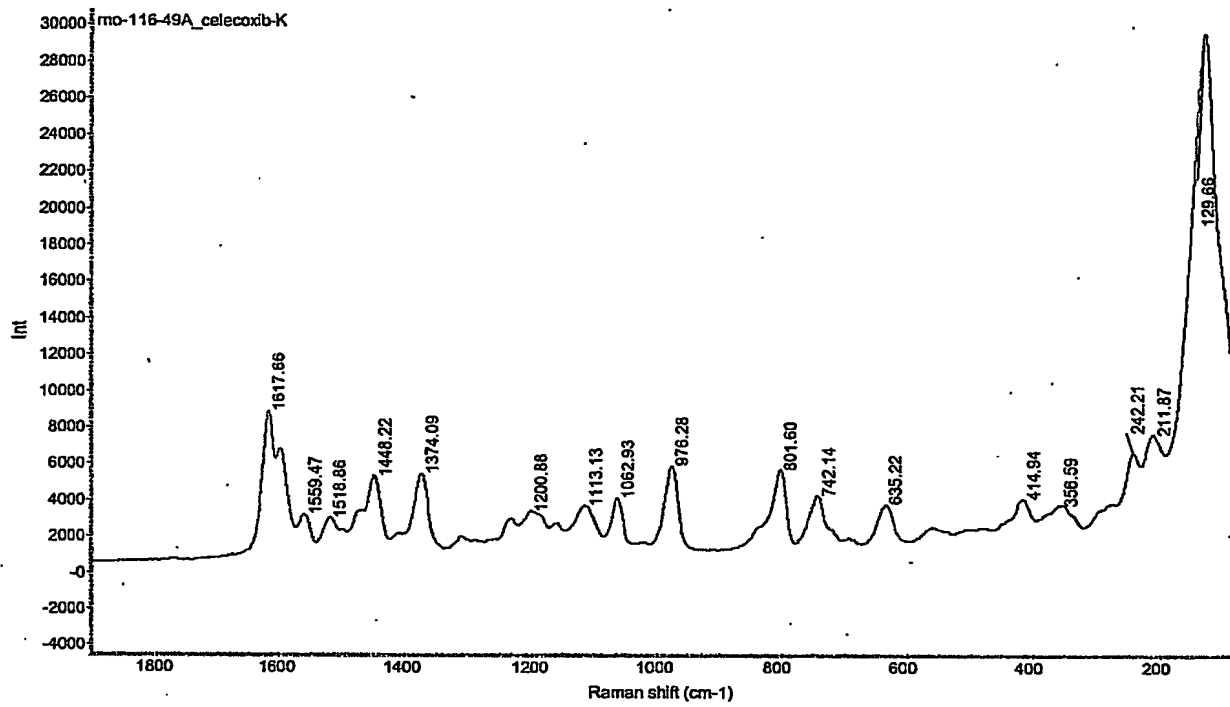


FIGURE 20

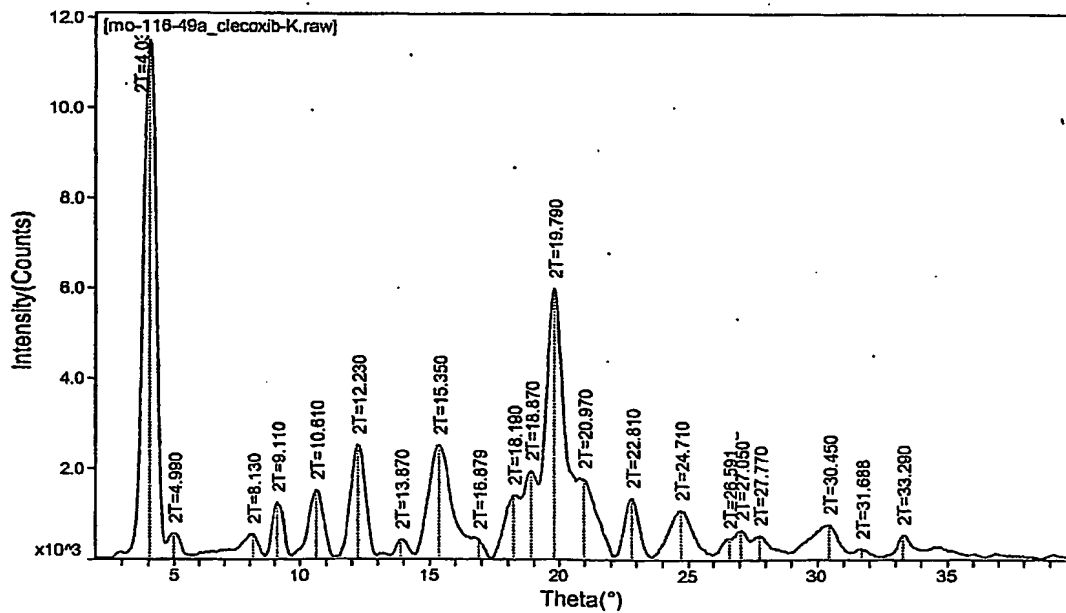


FIGURE 21

Sample: MO-116-55D\_celecoxib-K

Size: 5.4470 mg

Method: Ramp

Comment: Residue from bottom phase, dried in nitrogen for 2 days

TGA

File: mo-116-55D\_celecoxibK\_bottom phase re...

Operator: MAO

Run Date: 13-Dec-02 11:50

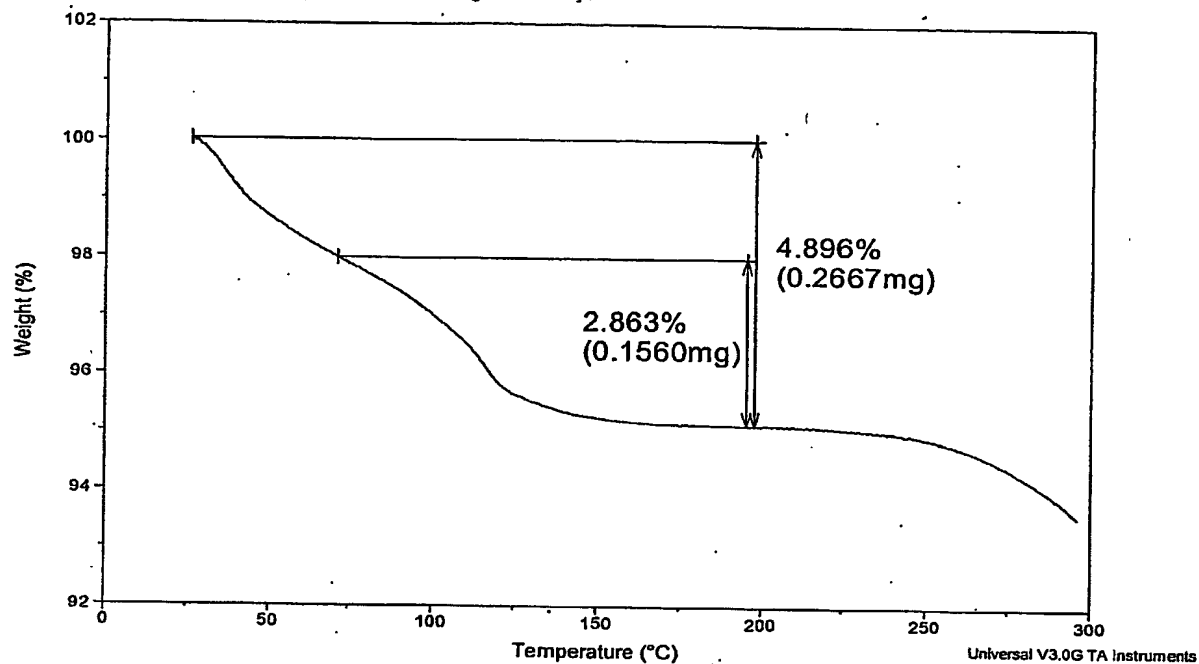


FIGURE 22

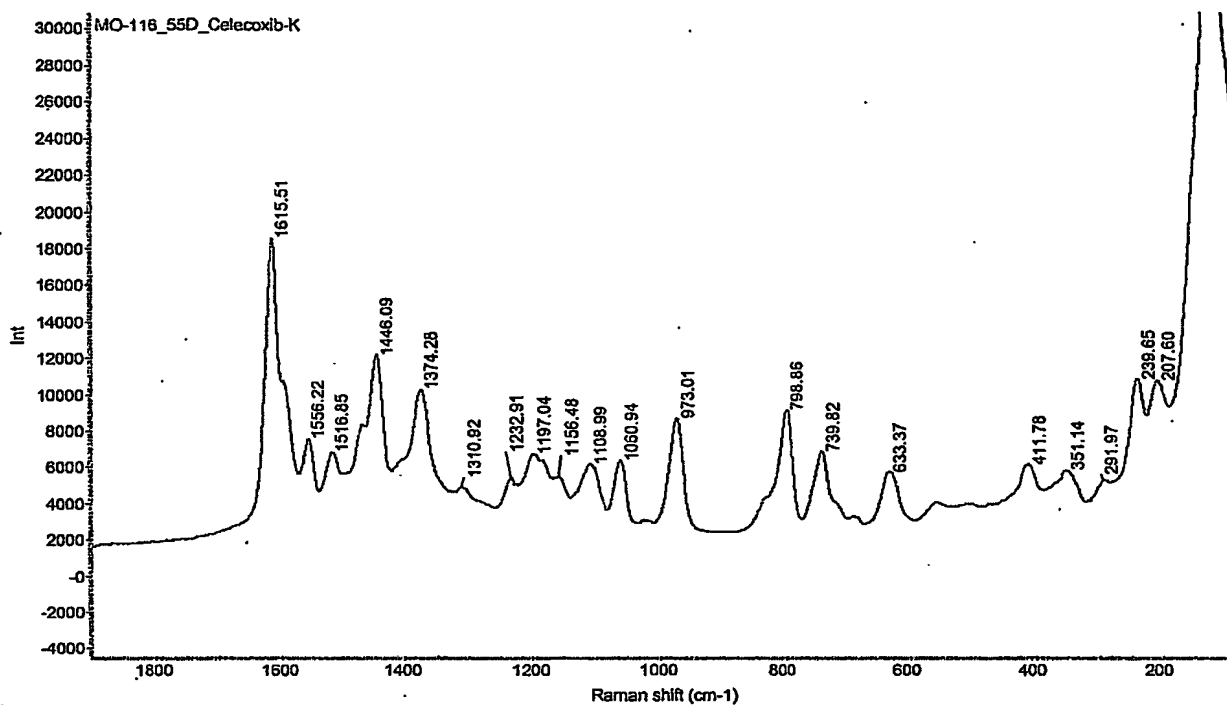


FIGURE 23

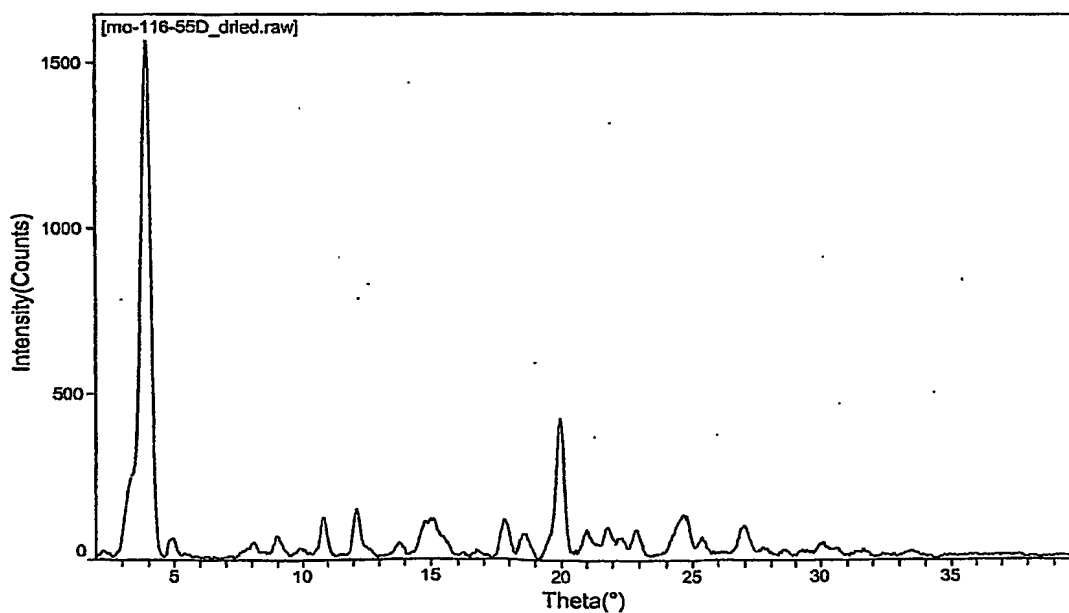


FIGURE 24

Sample: celecoxib-Ca\_dried  
Size: 3.4140 mg  
Method: Ramp  
Comment: dried in N2 overnight

TGA

File: V:\...mo-11-62A\_celecoxib-Ca.003  
Operator: MAO  
Run Date: 18-Dec-02 11:26

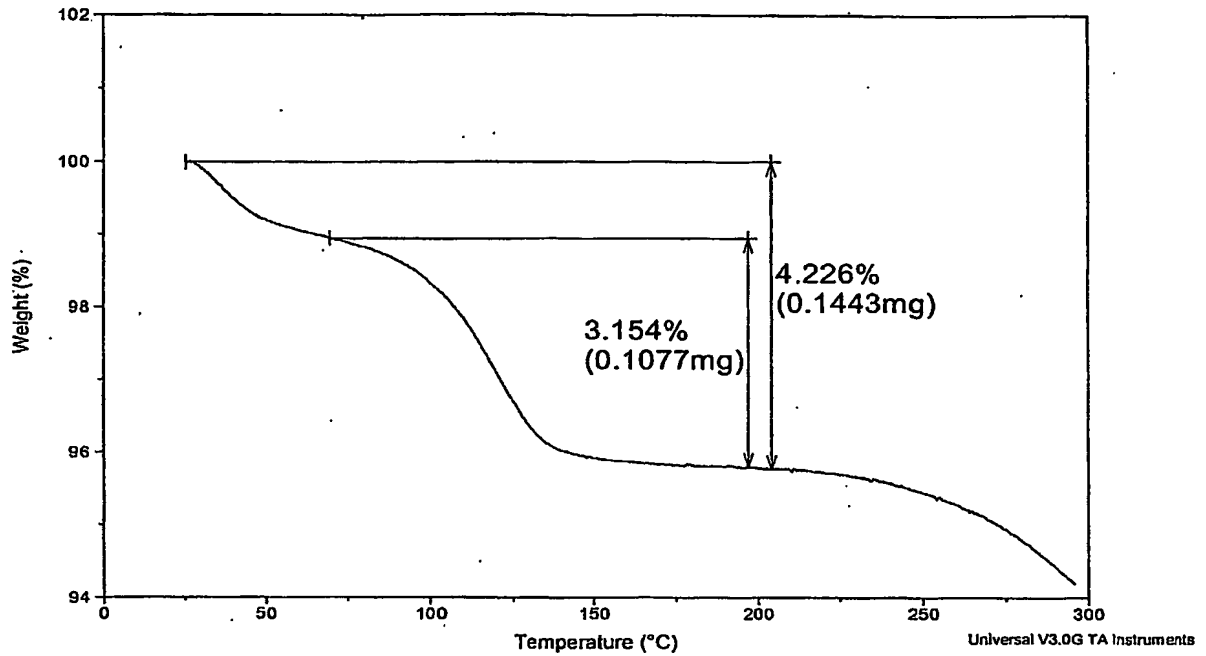


FIGURE 25

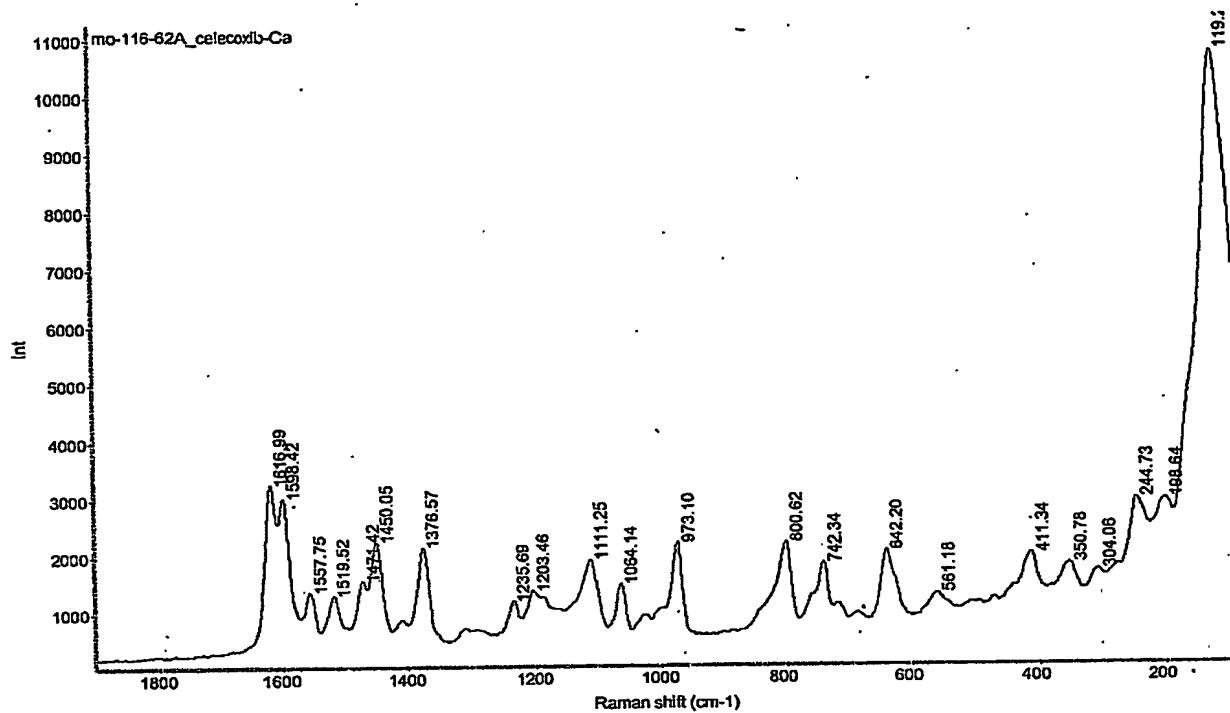


FIGURE 26



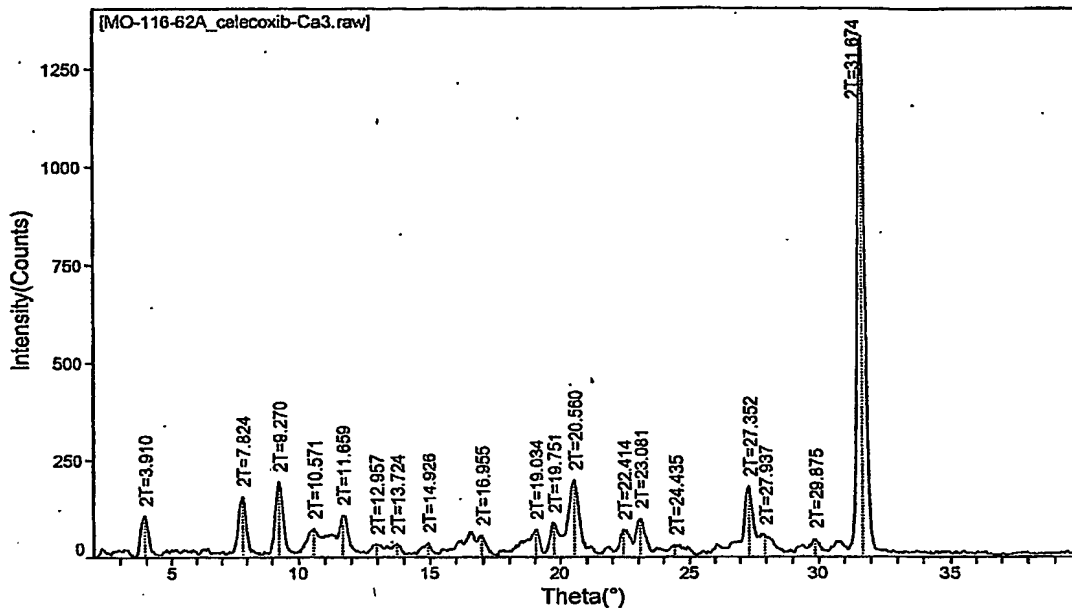


FIGURE 27

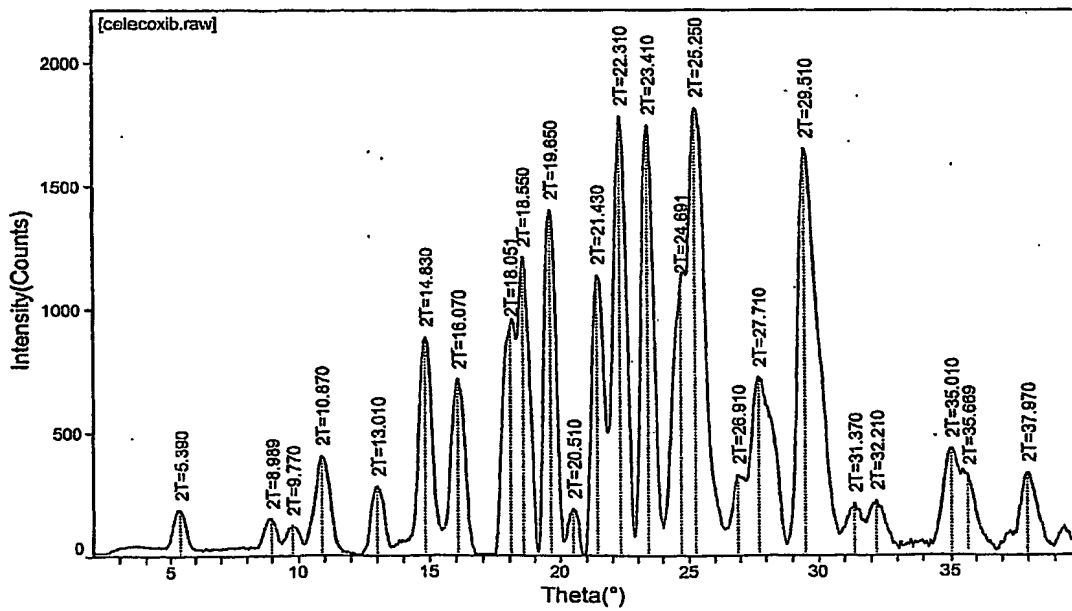


FIGURE 28

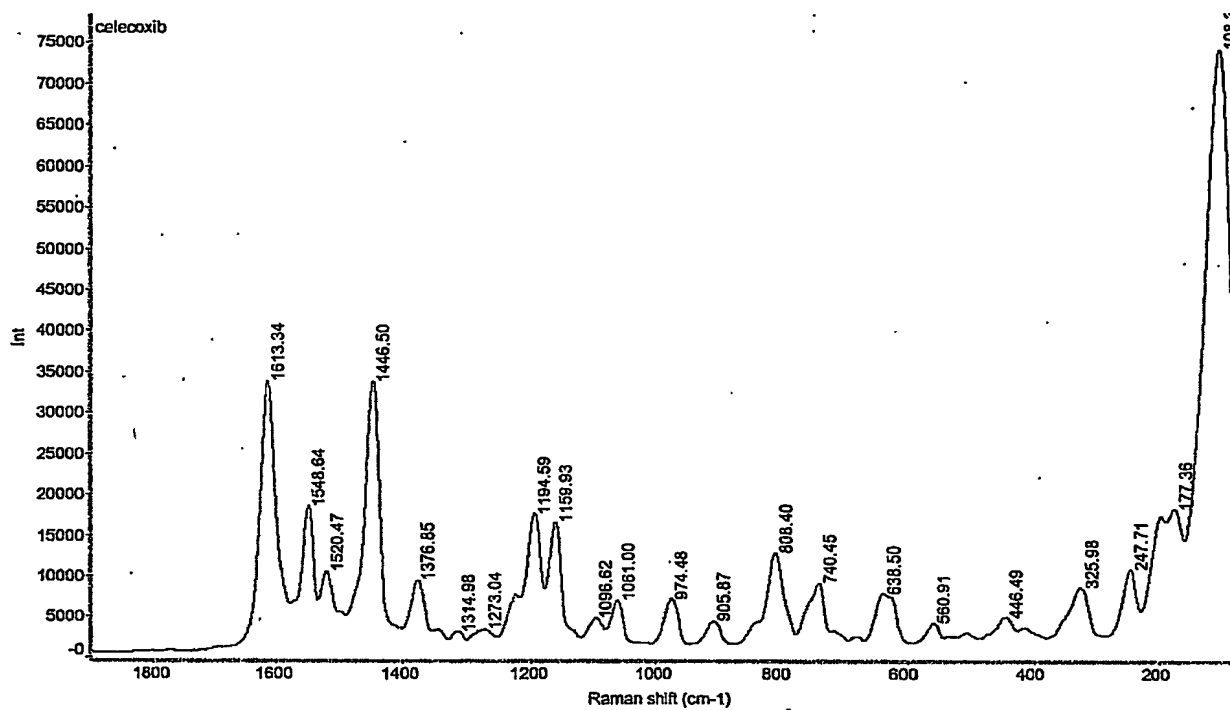


FIGURE 29

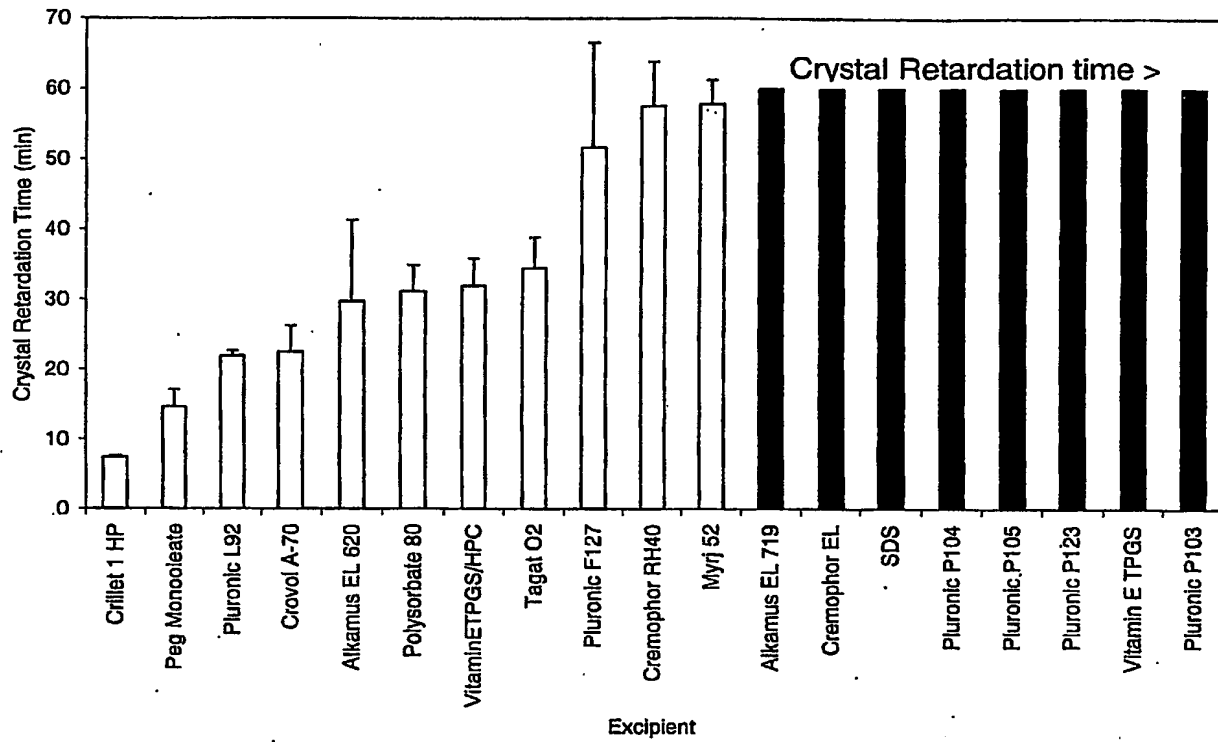


FIGURE 30

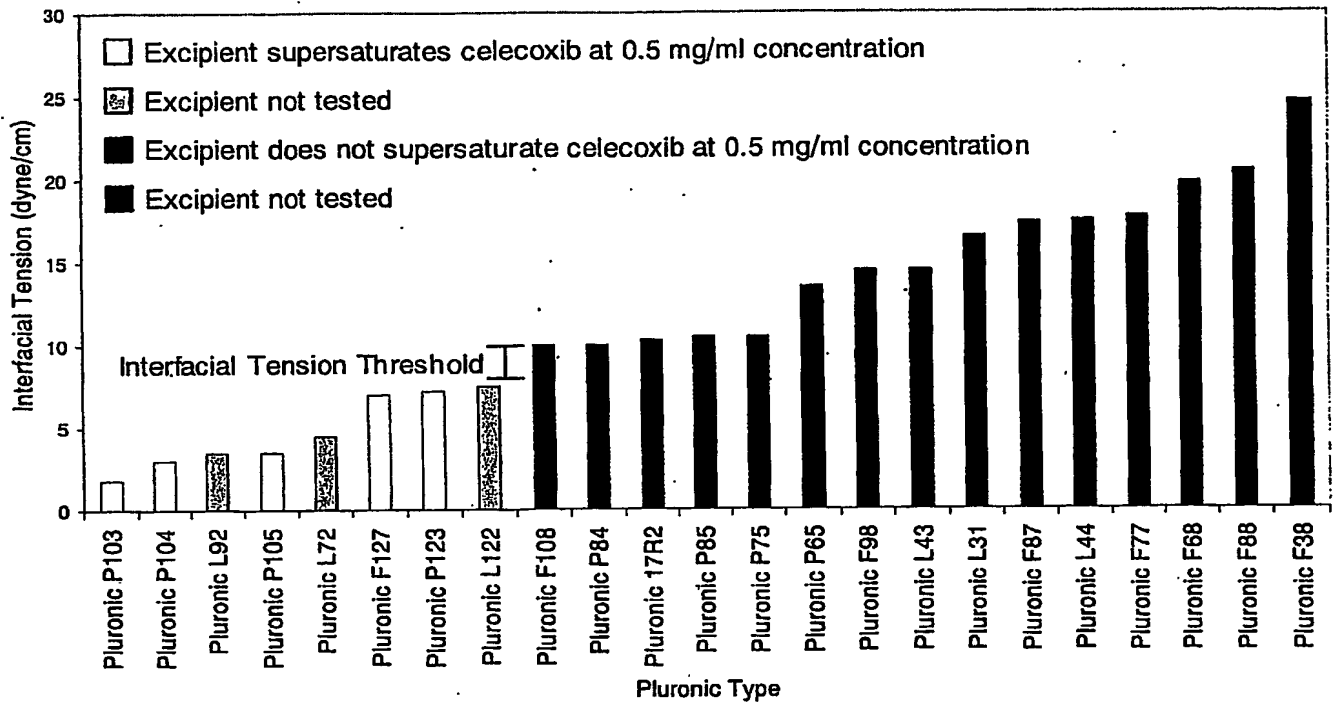
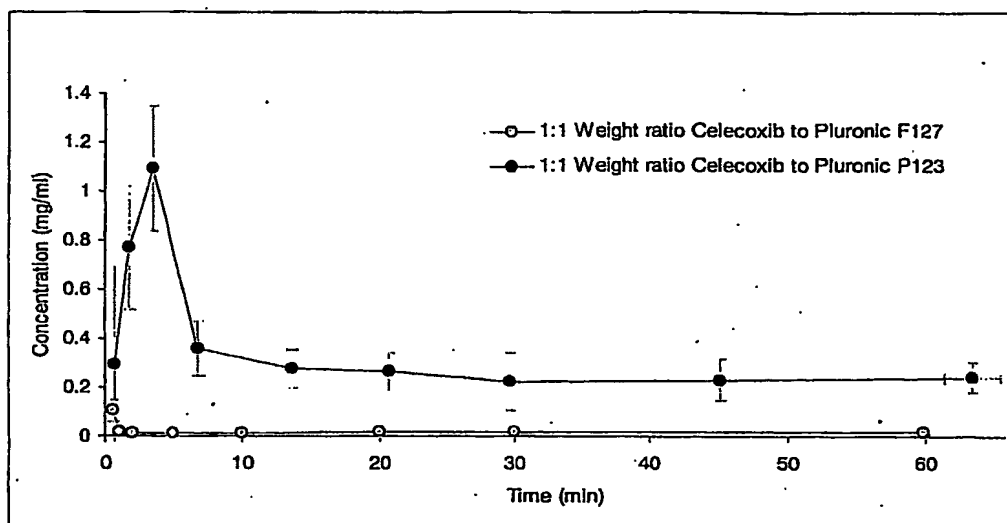
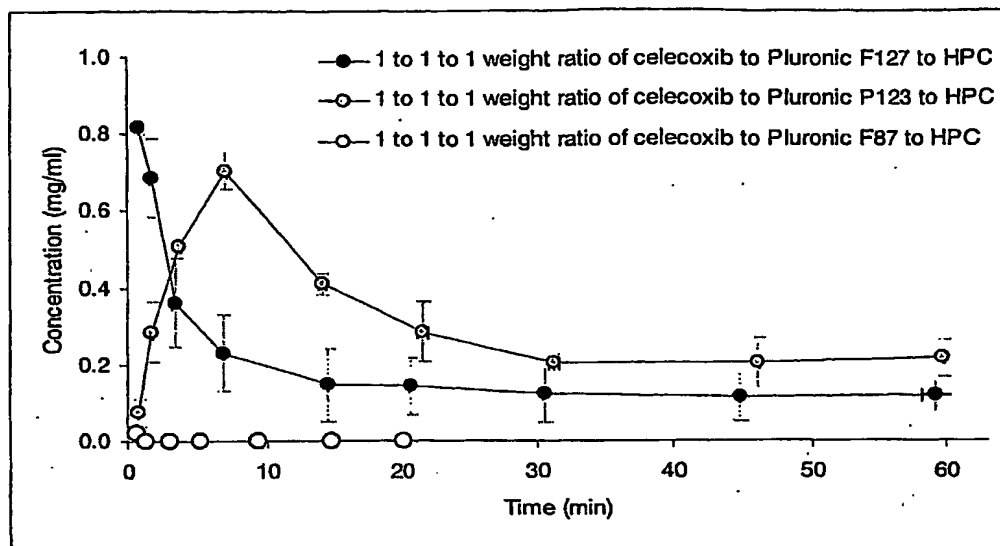
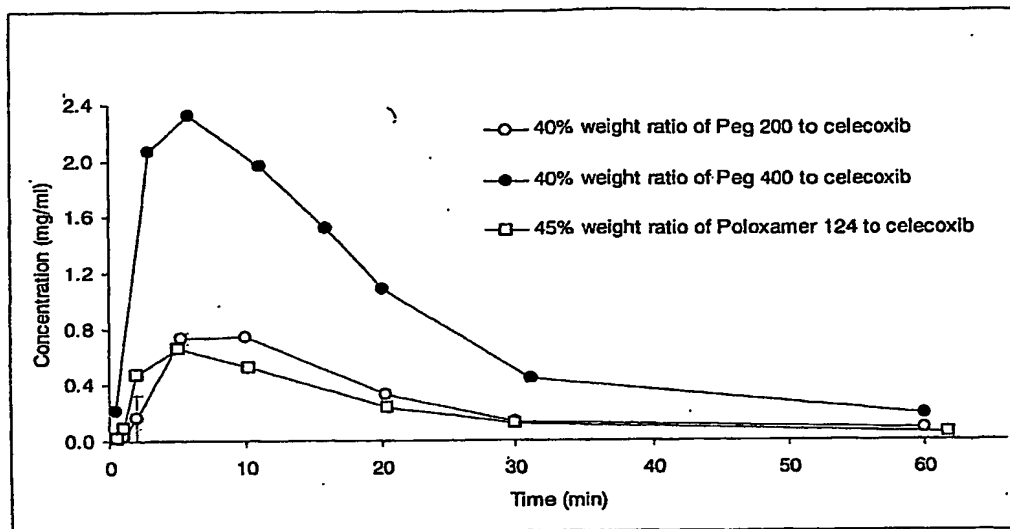
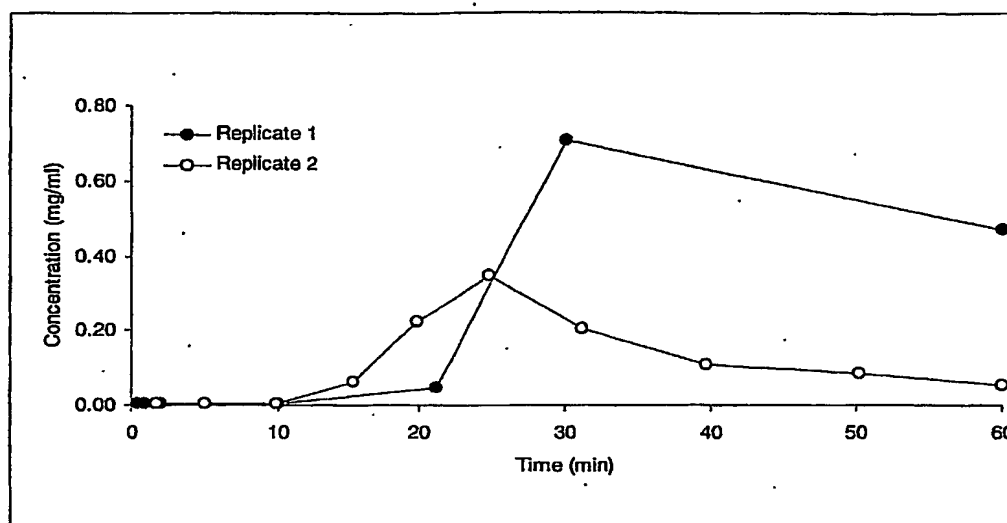


Figure 31

**Figure 32**

**Figure 33**

**Figure 34**



**Figure 35**